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MEDICAL SCIENCE UNDER DICTATORSHIP

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SCIENCE under dictatorship becomes subordinated to the guiding philosophy of the dictatorship. Irrespective of other ideologic trappings, the guiding philosophic principle of recent dictatorships, including that of the Nazis, has been Hegelian in that what has been considered "rational utility" and corresponding doctrine and planning has replaced moral, ethical and religious values. Nazi propaganda was highly effective in perverting public opinion and public conscience, in a remarkably short time. In the medical profession this expressed itself in a rapid decline in standards of professional ethics. Medical science in Nazi Germany collaborated with this Hegelian trend particularly in the following enterprises: the mass extermination of the chronically sick in the interest of saving "useless" expenses to the community as a whole; the mass extermination of those considered socially disturbing or racially and ideologically unwanted; the individual, inconspicuous extermination of those considered disloyal within the ruling group; and the ruthless use of "human experimental material" for medico-military research.

This paper discusses the origins of these activities, as well as their consequences upon the body social, and the motivation of those participating in them.

Preparatory Propaganda

Even before the Nazis took open charge in Germany, a propaganda barrage was directed against the traditional compassionate nineteenth-century attitudes toward the chronically ill, and for the adoption of a utilitarian, Hegelian point of view. Sterilization and euthanasia of persons with chronic mental illnesses was discussed at a meeting of Bavarian psychiatrists in 1931.[1] By 1936 extermination of the physically or socially unfit was so openly accepted that its practice was mentioned incidentally in an article published in an official German medical journal.[2]

Lay opinion was not neglected in this campaign. Adults were propagandized by motion pictures, one of which, entitled "I Accuse," deals entirely with euthanasia. This film depicts the life history of a woman suffering from multiple sclerosis; in it her husband, a doctor, finally kills her to the accompaniment of soft piano music rendered by a sympathetic colleague in an adjoining room. Acceptance of this ideology was implanted even in the children. A widely used high-school mathematics text, "Mathematics in the Service of National Political Education,"[3] includes problems stated in distorted terms of the cost of caring for and rehabilitating the chronically sick and crippled. One of the problems asked, for instance, how many new housing units could be built and how many marriage-allowance loans could be given to newly wedded couples for the amount of money it cost the state to care for "the crippled, the criminal and the insane."

Euthanasia

The first direct order for euthanasia was issued by Hitler on September 1, 1939, and an organization was set up to execute the program. Dr. Karl Brandt headed the medical section, and Phillip Bouhler the administrative section. All state institutions were required to report on patients who had been ill five years or more and who were unable to work, by filling out questionnaires giving name, race, marital status, nationality, next of kin, whether regularly visited and by whom, who bore financial responsibility and so forth. The decision regarding which patients should be killed was made entirely on the basis of this brief information by expert consultants, most of whom were professors of psychiatry in the key universities. These consultants never saw the patients themselves. The thoroughness of their scrutiny can be appraised by the work of one expert, who between November 14 and December 1, 1940, evaluated 2109 questionnaires.

These questionnaires were collected by a "Realm's Work Committee of Institutions for Cure and Care."[4] A parallel organization devoted exclusively to the killing of children was known by the similarly euphemistic name of "Realm's Committee for Scientific Approach to Severe Illness Due to Heredity and Constitution." The "Charitable

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Transport Company for the Sick" transported patients to the killing centers, and the "Charitable Foundation for Institutional Care" was in charge of collecting the cost of the killings from the relatives, without, however, informing them what the charges were for; in the death certificates the cause of death was falsified.

What these activities meant to the population at large was well expressed by a few hardy souls who dared to protest. A member of the court of appeals at Frankfurt-am-Main wrote in December, 1939:

> There is constant discussion of the question of the destruction of socially unfit life — in the places where there are mental institutions, in neighboring towns, sometimes over a large area, throughout the Rhineland, for example. The people have come to recognize the vehicles in which the patients are taken from their original institution to the intermediate institution and from there to the liquidation institution. I am told that when they see these buses even the children call out: "They're taking some more people to be gassed." From Limburg it is reported that every day from one to three buses with shades drawn pass through on the way from Weilmunster to Hadamar, delivering inmates to the liquidation institution there. According to the stories the arrivals are immediately stripped to the skin, dressed in paper shirts, and forthwith taken to a gas chamber, where they are liquidated with hydrocyanic acid gas and an added anesthetic. The bodies are reported to be moved to a combustion chamber by means of a conveyor belt, six bo ies to a furnace. The resulting ashes are then distributed into six urns which are shipped to the families. The heavy smoke from the crematory building is said to be visible over Hadamar every day. There is talk, furthermore, that in some cases heads and other portions of the body are removed for anatomical examination. The people working at this liquidation job in the institutions are said to be assigned from other areas and are shunned completely by the populace. This personnel is described as frequenting the bars at night and drinking heavily. Quite apart from these overt incidents that exercise the imagination of the people, they are disquieted by the question of whether old folk who have worked hard all their lives and may merely have come into their dotage are also being liquidated. There is talk that the homes for the aged are to be cleaned out too. The people are said to be waiting for legislative regulation providing some orderly method that will insure especially that the aged feeble-minded are not included in the program.

Here one sees what "euthanasia" means in actual practice. According to the records, 275,000 people were put to death in these killing centers. Ghastly as this seems, it should be realized that this program was merely the entering wedge for exterminations of far greater scope in the political program for genocide of conquered nations and the racially unwanted. The methods used and personnel trained in the killing centers for the chronically sick became the nucleus of the much larger centers in the East, where the plan was to kill all Jews and Poles and to cut down the Russian population by 30,000,000.

The original program developed by Nazi hotheads included also the genocide of the English, with the provision that the English males were to be used as laborers in the vacated territories in the East, there to be worked to death, whereas the English females were to be brought into Germany to improve the qualities of the German race. (This was indeed a peculiar admission on the part of the German eugenists.)

In Germany the exterminations included the mentally defective, psychotics (particularly schizophrenics), epileptics and patients suffering from infirmities of old age and from various organic neurologic disorders such as infantile paralysis, Parkinsonism, multiple sclerosis and brain tumors. The technical arrangements, methods and training of the killer personnel were under the direction of a committee of physicians and other experts headed by Dr. Karl Brandt. The mass killings were first carried out with carbon monoxide gas, but later cyanide gas ("cyclon B") was found to be more effective. The idea of camouflaging the gas chambers as shower baths was developed by Brack, who testified before Judge Sebring that the patients walked in calmly, deposited their towels and stood with their little pieces of soap under the shower outlets, waiting for the water to start running. This statement was ample rebuttal of his claim that only the most severely regressed patients among the mentally sick and only the moribund ones among the physically sick were exterminated. In truth, all those unable to work and considered nonrehabilitable were killed.

All but their squeal was utilized. However, the program grew so big that even scientists who hoped to benefit from the treasure of material supplied by this totalitarian method were disappointed. A neuropathologist, Dr. Hallervorden, who had obtained 500 brains from the killing centers for the insane, gave me a vivid first-hand account.[6] The Charitable Transport Company for the Sick brought the brains in batches of 150 to 250 at a time. Hallervorden stated:

> There was wonderful material among those brains, beautiful mental defectives, malformations and early infantile diseases. I accepted those brains of course. Where they came from and how they came to me was really none of my business.

In addition to the material he wanted, all kinds of other cases were mixed in, such as patients suffering from various types of Parkinsonism, simple depressions, involutional depressions and brain tumors, and all kinds of other illnesses, including psychopathy that had been difficult to handle:

> These were selected from the various wards of the institutions according to an excessively simple and quick method. Most institutions did not have enough physicians, and what physicians there were were either too busy or did not care, and they delegated the selection to the nurses and attendants. Whoever looked sick or was otherwise a problem was put on a list and was transported to the killing center. The worst thing about this business was that it produced a certain brutalization of the nursing personnel. They got to simply picking out those whom they did not like, and the doctors had so many patients that they did not even know them, and put their names on the list.

Of the patients thus killed, only the brains were sent to Dr. Hallervorden; they were killed in such

large numbers that autopsies of the bodies were not feasible. That, in Dr. Hallervorden's opinion, greatly reduced the scientific value of the material. The brains, however, were always well fixed and suspended in formalin, exactly according to his instructions. He thinks that the cause of psychiatry was permanently injured by these activities, and that psychiatrists have lost the respect of the German people forever. Dr. Hallervorden concluded: "Still, there were interesting cases in this material."

In general only previously hospitalized patients were exterminated for reasons of illness. An exception is a program carried out in a northwestern district of Poland, the "Warthegau," where a health survey of the entire population was made by an "S.S. X-Ray Battalion" headed by Professor Hohlfelder, radiologist of the University of Frankfurt-am-Main. Persons found to be infected with tuberculosis were carted off to special extermination centers.

It is rather significant that the German people were considered by their Nazi leaders more ready to accept the exterminations of the sick than those for political reasons. It was for that reason that the first exterminations of the latter group were carried out under the guise of sickness. So-called "psychiatric experts" were dispatched to survey the inmates of camps with the specific order to pick out members of racial minorities and political offenders from occupied territories and to dispatch them to killing centers with specially made diagnoses such as that of "inveterate German hater" applied to a number of prisoners who had been active in the Czech underground.

Certain classes of patients with mental diseases who were capable of performing labor, particularly members of the armed forces suffering from psychopathy or neurosis, were sent to concentration camps to be worked to death, or to be reassigned to punishment battalions and to be exterminated in the process of removal of mine fields.[6]

A large number of those marked for death for political or racial reasons were made available for "medical" experiments involving the use of involuntary human subjects. From 1942 on, such experiments carried out in concentration camps were openly presented at medical meetings. This program included "terminal human experiments," a term introduced by Dr. Rascher to denote an experiment so designed that its successful conclusion depended upon the test person's being put to death.

The Science of Annihilation

A large part of this research was devoted to the science of destroying and preventing life, for which I have proposed the term "ktenology," the science of killing.[7-9] In the course of this ktenologic research, methods of mass killing and mass sterilization were investigated and developed for use against non-German peoples or Germans who were considered useless.

Sterilization methods were widely investigated, but proved impractical in experiments conducted in concentration camps. A rapid method developed for sterilization of females, which could be accomplished in the course of a regular health examination, was the intra-uterine injection of various chemicals. Numerous mixtures were tried, some with iodopine and others containing barium; another was most likely silver nitrate with iodized oil, because the result could be ascertained by x-ray examination. The injections were extremely painful, and a number of women died in the course of the experiments. Professor Karl Clauberg reported that he had developed a method at the Auschwitz concentration camp by which he could sterilize 1000 women in one day.

Another method of sterilization, or rather castration, was proposed by Viktor Brack especially for conquered populations. His idea was that x-ray machinery could be built into desks at which the people would have to sit, ostensibly to fill out a questionnaire requiring five minutes; they would be sterilized without being aware of it. This method failed because experiments carried out on 100 male prisoners brought out the fact that severe x-ray burns were produced on all subjects. In the course of this research, which was carried out by Dr. Horst Schuman, the testicles of the victims were removed for histologic examination two weeks later. I myself examined 4 castrated survivors of this ghastly experiment. Three had extensive necrosis of the skin near the genitalia, and the other an extensive necrosis of the urethra. Other experiments in sterilization used an extract of the plant *Caladium seguinum*, which had been shown in animal studies by Madaus and his co-workers[10, 11] to cause selective necrosis of the germinal cells of the testicles as well as the ovary.

The development of methods for rapid and inconspicuous individual execution was the objective of another large part of the ktenologic research. These methods were to be applied to members of the ruling group, including the SS itself, who were suspected of disloyalty. This, of course, is an essential requirement in a dictatorship, in which "cutthroat competition" becomes a grim reality, and any hint of faintheartedness or lack of enthusiasm for the methods of totalitarian rule is considered a threat to the entire group.

Poisons were the subject of many of these experiments. A research team at the Buchenwald concentration camp, consisting of Drs. Joachim Mrugowsky, Erwin Ding-Schuler and Waldemar Hoven, developed the most widely used means of individual execution under the guise of medical treatment — namely, the intravenous injection of phenol or gasoline. Several alkaloids were also investigated, among them aconitine, which was used

by Dr. Hoven to kill several imprisoned former fellow SS men who were potential witnesses against the camp commander, Koch, then under investigation by the SS. At the Dachau concentration camp Dr. Rascher developed the standard cyanide capsules, which could be easily bitten through, either deliberately or accidentally, if mixed with certain foods, and which, ironically enough, later became the means with which Himmler and Goering killed themselves. In connection with these poison experiments there is an interesting incident of characteristic sociologic significance. When Dr. Hoven was under trial by the SS the investigating SS judge, Dr. Morgen, proved Hoven's guilt by feeding the poison found in Dr. Hoven's possession to a number of Russian prisoners of war; these men died with the same symptoms as the SS men murdered by Dr. Hoven. This worthy judge was rather proud of this efficient method of proving Dr. Hoven's guilt and appeared entirely unaware of the fact that in the process he had committed murder himself.

Poisons, however, proved too obvious or detectable to be used for the elimination of high-ranking Nazi party personnel who had come into disfavor, or of prominent prisoners whose deaths should appear to stem from natural causes. Phenol or gasoline, for instance, left a telltale odor with the corpse. For this reason a number of more subtle methods were devised. One of these was artificial production of septicemia. An intramuscular injection of 1 cc. of pus, containing numerous chains of streptococci, was the first step. The site of injection was usually the inside of the thigh, close to the adductor canal. When an abscess formed it was tapped, and 3 cc. of the creamy pus removed was injected intravenously into the patient's opposite arm. If the patient then died from septicemia, the autopsy proved that death was caused by the same organism that had caused the abscess. These experiments were carried out in many concentration camps. At the Dachau camp the subjects were almost exclusively Polish Catholic priests. However, since this method did not always cause death, sometimes resulting merely in a local abscess, it was considered inefficient, and research was continued with other means but along the same lines.

The final triumph of the part of ktenologic research aimed at finding a method of inconspicuous execution that would produce autopsy findings indicative of death from natural causes was the development of repeated intravenous injections of suspensions of live tubercle bacilli, which brought on acute miliary tuberculosis within a few weeks. This method was produced by Professor Dr. Heissmeyer, who was one of Dr. Gebhardt's associates at the SS hospital of Hohenlychen. As a means of further camouflage, so that the SS at large would not suspect the purpose of these experiments, the preliminary tests for the efficacy of this method were performed exclusively on children imprisoned in the Neuengamme concentration camp.

For use in "medical" executions of prisoners and of members of the SS and other branches of the German armed forces the use of simple lethal injections, particularly phenol injections, remained the instrument of choice. Whatever methods he used, the physician gradually became the unofficial executioner, for the sake of convenience, informality and relative secrecy. Even on German submarines it was the physician's duty to execute the troublemakers among the crew by lethal injections.

Medical science has for some time been an instrument of military power in that it preserved the health and fighting efficiency of troops. This essentially defensive purpose is not inconsistent with the ethical principles of medicine. In World War I the German empire had enlisted medical science as an instrument of aggressive military power by putting it to use in the development of gas warfare. It was left to the Nazi dictatorship to make medical science into an instrument of political power — a formidable, essential tool in the complete and effective manipulation of totalitarian control. This should be a warning to all civilized nations, and particularly to individuals who are blinded by the "efficiency" of a totalitarian rule, under whatever name.

This entire body of research as reported so far served the master crime to which the Nazi dictatorship was committed — namely, the genocide of non-German peoples and the elimination by killing, in groups or singly, of Germans who were considered useless or disloyal. In effecting the two parts of this program, Himmler demanded and received the co-operation of physicians and of German medical science. The result was a significant advance in the science of killing, or ktenology.

Medicomilitary Research

Another chapter in Nazi scientific research was that aimed to aid the military forces. Many of these ideas originated with Himmler, who fancied himself a scientist.

When Himmler learned that the cause of death of most SS men on the battlefield was hemorrhage, he instructed Dr. Sigmund Rascher to search for a blood coagulant that might be given before the men went into action. Rascher tested this coagulant when it was developed by clocking the number of drops emanating from freshly cut amputation stumps of living and conscious prisoners at the crematorium of Dachau concentration camp and by shooting Russian prisoners of war through the spleen.

Live dissections were a feature of another experimental study designed to show the effects of explosive decompression.[12-14] A mobile decompression chamber was used. It was found that when subjects were made to descend from altitudes of 40,000 to 60,000 feet without oxygen, severe symptoms

of cerebral dysfunction occurred — at first convulsions, then unconsciousness in which the body was hanging limp and later, after wakening, temporary blindness, paralysis or severe confusional twilight states. Rascher, who wanted to find out whether these symptoms were due to anoxic changes or to other causes, did what appeared to him the most simple thing: he placed the subjects of the experiment under water and dissected them while the heart was still beating, demonstrating air embolism in the blood vessels of the heart, liver, chest wall and brain.

Another part of Dr. Rascher's research, carried out in collaboration with Holzloehner and Finke, concerned shock from exposure to cold.[15] It was known that military personnel generally did not survive immersion in the North Sea for more than sixty to a hundred minutes. Rascher therefore attempted to duplicate these conditions at Dachau concentration camp and used about 300 prisoners in experiments on shock from exposure to cold; of these 80 or 90 were killed. (The figures do not include persons killed during mass experiments on exposure to cold outdoors.) In one report on this work Rascher asked permission to shift these experiments from Dachau to Auschwitz, a larger camp where they might cause less disturbance because the subjects shrieked from pain when their extremities froze white. The results, like so many of those obtained in the Nazi research program, are not dependable. In his report Rascher stated that it took from fifty-three to a hundred minutes to kill a human being by immersion in ice water — a time closely in agreement with the known survival period in the North Sea. Inspection of his own experimental records and statements made to me by his close associates showed that it actually took from eighty minutes to five or six hours to kill an undressed person in such a manner, whereas a man in full aviator's dress took six or seven hours to kill. Obviously, Rascher dressed up his findings to forestall criticism, although any scientific man should have known that during actual exposure many other factors, including greater convection of heat due to the motion of water, would affect the time of survival.

Another series of experiments gave results that might have been an important medical contribution if an important lead had not been ignored. The efficacy of various vaccines and drugs against typhus was tested at the Buchenwald and Natzweiler concentration camps. Prevaccinated persons and nonvaccinated controls were injected with live typhus rickettsias, and the death rates of the two series compared. After a certain number of passages, the Matelska strain of typhus rickettsia proved to become avirulent for man. Instead of seizing upon this as a possibility to develop a live vaccine, the experimenters, including the chief consultant, Professor Gerhard Rose, who should have known better, were merely annoyed at the fact that the controls did not die either, discarded this strain and continued testing their relatively ineffective dead vaccines against a new virulent strain. This incident shows that the basic unconscious motivation and attitude has a great influence in determining the scientist's awareness of the phenomena that pass through his vision.

Sometimes human subjects were used for tests that were totally unnecessary, or whose results could have been predicted by simple chemical experiments. For example, 90 gypsies were given unaltered sea water and sea water whose taste was camouflaged as their sole source of fluid, apparently to test the well known fact that such hypertonic saline solutions given as the only source of supply of fluid will cause severe physical disturbance or death within six to twelve days. These persons were subjected to the tortures of the damned, with death resulting in at least 2 cases.

Heteroplastic transplantation experiments were carried out by Professor Dr. Karl Gebhardt at Himmler's suggestion. Whole limbs — shoulder, arm or leg — were amputated from live prisoners at Ravensbrueck concentration camp, wrapped in sterile moist dressings and sent by automobile to the SS hospital at Hohenlychen, where Professor Gebhardt busied himself with a futile attempt at heteroplastic transplantation. In the meantime the prisoners deprived of a limb were usually killed by lethal injection.

One would not be dealing with German science if one did not run into manifestations of the collector's spirit. By February, 1942, it was assumed in German scientific circles that the Jewish race was about to be completely exterminated, and alarm was expressed over the fact that only very few specimens of skulls and skeletons of Jews were at the disposal of science. It was therefore proposed that a collection of 150 body casts and skeletons of Jews be preserved for perusal by future students of anthropology. Dr. August Hirt, professor of anatomy at the University of Strassburg, declared himself interested in establishing such a collection at his anatomic institute. He suggested that captured Jewish officers of the Russian armed forces be included, as well as females from Auschwitz concentration camp; that they be brought alive to Natzweiler concentration camp near Strassburg; and that after "their subsequently induced death — care should be taken that the heads not be damaged [sic]" the bodies be turned over to him at the anatomic institute of the University of Strassburg. This was done. The entire collection of bodies and the correspondence pertaining to it fell into the hands of the United States Army.

One of the most revolting experiments was the testing of sulfonamides against gas gangrene by Professor Gebhardt and his collaborators, for which young women captured from the Polish Resistance

Movement served as subjects. Necrosis was produced in a muscle of the leg by ligation and the wound was infected with various types of gas-gangrene bacilli; frequently, dirt, pieces of wood and glass splinters were added to the wound. Some of these victims died, and others sustained severe mutilating deformities of the leg.

Motivation

An important feature of the experiments performed in concentration camps is the fact that they not only represented a ruthless and callous pursuit of legitimate scientific goals but also were motivated by rather sinister practical ulterior political and personal purposes, arising out of the requirements and problems of the administration of totalitarian rule.

Why did men like Professor Gebhardt lend themselves to such experiments? The reasons are fairly simple and practical, no surprise to anyone familiar with the evidence of fear, hostility, suspicion, rivalry and intrigue, the fratricidal struggle euphemistically termed the "self-selection of leaders," that went on within the ranks of the ruling Nazi party and the SS. The answer was fairly simple and logical. Dr. Gebhardt performed these experiments to clear himself of the suspicion that he had been contributing to the death of SS General Reinhard ("The Hangman") Heydrich, either negligently or deliberately, by failing to treat his wound infection with sulfonamides. After Heydrich died from gas gangrene, Himmler himself told Dr. Gebhardt that the only way in which he could prove that Heydrich's death was "fate determined" was by carrying out a "large-scale experiment" in prisoners, which would prove or disprove that people died from gas gangrene irrespective of whether they were treated with sulfonamides or not.

Dr. Sigmund Rascher did not become the notorious vivisectionist of Dachau concentration camp and the willing tool of Himmler's research interests until he had been forbidden to use the facilities of the Pathological Institute of the University of Munich because he was suspected of having Communist sympathies. Then he was ready to go all out and to do anything merely to regain acceptance by the Nazi party and the SS.

These cases illustrate a method consciously and methodically used in the SS, an age-old method used by criminal gangs everywhere: that of making suspects of disloyalty clear themselves by participation in a crime that would definitely and irrevocably tie them to the organization. In the SS this process of reinforcement of group cohesion was called "Blutkitt' (blood-cement), a term that Hitler himself is said to have obtained from a book on Genghis Khan in which this technic was emphasized.

The important lesson here is that this motivation, with which one is familiar in ordinary crimes, applies also to war crimes and to ideologically conditioned crimes against humanity — namely, that fear and cowardice, especially fear of punishment or of ostracism by the group, are often more important motives than simple ferocity or aggressiveness.

The Early Change in Medical Attitudes

Whatever proportions these crimes finally assumed, it became evident to all who investigated them that they had started from small beginnings. The beginnings at first were merely a subtle shift in emphasis in the basic attitude of the physicians. It started with the acceptance of the attitude, basic in the euthanasia movement, that there is such a thing as life not worthy to be lived. This attitude in its early stages concerned itself merely with the severely and chronically sick. Gradually the sphere of those to be included in this category was enlarged to encompass the socially unproductive, the ideologically unwanted, the racially unwanted and finally all non-Germans. But it is important to realize that the infinitely small wedged-in lever from which this entire trend of mind received its impetus was the attitude toward the nonrehabilitable sick.

It is, therefore, this subtle shift in emphasis of the physicians' attitude that one must thoroughly investigate. It is a recent significant trend in medicine, including psychiatry, to regard prevention as more important than cure. Observation and recognition of early signs and symptoms have become the basis for prevention of further advance of disease.[8]

In looking for these early signs one may well retrace the early steps of propaganda on the part of the Nazis in Germany as well as in the countries that they overran and in which they attempted to gain supporters by means of indoctrination, seduction and propaganda.

The Example of Successful Resistance by the Physicians of the Netherlands

There is no doubt that in Germany itself the first and most effective step of propaganda within the medical profession was the propaganda barrage against the useless, incurably sick described above. Similar, even more subtle efforts were made in some of the occupied countries. It is to the everlasting honor of the medical profession of Holland that they recognized the earliest and most subtle phases of this attempt and rejected it. When Seiss-Inquart, Reich Commissar for the Occupied Netherlands Territories, wanted to draw the Dutch physicians into the orbit of the activities of the German medical profession, he did not tell them "You must send your chronic patients to death factories" or "You must give lethal injections at Government request in your offices," but he couched his order in most careful and superficially acceptable terms. One of the paragraphs in the order of the Reich Commissar of the Netherlands Territories concerning the Netherlands doctors of

19 December 1941 reads as follows: "It is the duty of the doctor, through advice and effort, conscientiously and to his best ability, to assist as helper the person entrusted to his care in the maintenance, improvement and re-establishment of his vitality, physical efficiency and health. The accomplishment of this duty is a public task."[16] The physicians of Holland rejected this order unanimously because they saw what it actually meant — namely, the concentration of their efforts on mere rehabilitation of the sick for useful labor, and abolition of medical secrecy. Although on the surface the new order appeared not too grossly unacceptable, the Dutch physicians decided that it is the first, although slight, step away from principle that is the most important one. The Dutch physicians declared that they would not obey this order. When Seiss-Inquart threatened them with revocation of their licenses, they returned their licenses, removed their shingles and, while seeing their own patients secretly, no longer wrote death or birth certificates. Seiss-Inquart retraced his steps and tried to cajole them — still to no effect. Then he arrested 100 Dutch physicians and sent them to concentration camps. The medical profession remained adamant and quietly took care of their widows and orphans, but would not give in. Thus it came about that not a single euthanasia or nontherapeutic sterilization was recommended or participated in by any Dutch physician. They had the foresight to resist before the first step was taken, and they acted unanimously and won out in the end. It is obvious that if the medical profession of a small nation under the conqueror's heel could resist so effectively the German medical profession could likewise have resisted had they not taken the fatal first step. It is the first seemingly innocent step away from principle that frequently decides a career of crime. Corrosion begins in microscopic proportions.

The Situation in the United States

The question that this fact prompts is whether there are any danger signs that American physicians have also been infected with Hegelian, cold-blooded, utilitarian philosophy and whether early traces of it can be detected in their medical thinking that may make them vulnerable to departures of the type that occurred in Germany. Basic attitudes must be examined dispassionately. The original concept of medicine and nursing was not based on any rational or feasible likelihood that they could actually cure and restore but rather on an essentially maternal or religious idea. The Good Samaritan had no thought of nor did he actually care whether he could restore working capacity. He was merely motivated by the compassion in alleviating suffering. Bernal[17] states that prior to the advent of scientific medicine, the physician's main function was to give hope to the patient and to relieve his relatives of responsibility. Gradually, in all civilized countries, medicine has moved away from this position, strangely enough in direct proportion to man's actual ability to perform feats that would have been plain miracles in days of old. However, with this increased efficiency based on scientific development went a subtle change in attitude. Physicians have become dangerously close to being mere technicians of rehabilitation. This essentially Hegelian rational attitude has led them to make certain distinctions in the handling of acute and chronic diseases. The patient with the latter carries an obvious stigma as the one less likely to be fully rehabilitable for social usefulness. In an increasingly utilitarian society these patients are being looked down upon with increasing definiteness as unwanted ballast. A certain amount of rather open contempt for the people who cannot be rehabilitated with present knowledge has developed. This is probably due to a good deal of unconscious hostility, because these people for whom there seem to be no effective remedies have become a threat to newly acquired delusions of omnipotence.

Hospitals like to limit themselves to the care of patients who can be fully rehabilitated, and the patient whose full rehabilitation is unlikely finds himself, at least in the best and most advanced centers of healing, as a second-class patient faced with a reluctance on the part of both the visiting and the house staff to suggest and apply therapeutic procedures that are not likely to bring about immediately striking results in terms of recovery. I wish to emphasize that this point of view did not arise primarily within the medical profession, which has always been outstanding in a highly competitive economic society for giving freely and unstintingly of its time and efforts, but was imposed by the shortage of funds available, both private and public. From the attitude of easing patients with chronic diseases away from the doors of the best types of treatment facilities available to the actual dispatching of such patients to killing centers is a long but nevertheless logical step. Resources for the so-called incurable patient have recently become practically unavailable.

There has never in history been a shortage of money for the development and manufacture of weapons of war; there is and should be none now. The disproportion of monetary support for war and that available for healing and care is an anachronism in an era that has been described as the "enlightened age of the common man" by some observers. The comparable cost of jet planes and hospital beds is too obvious for any excuse to be found for a shortage of the latter. I trust that these remarks will not be misunderstood. I believe that armament, including jet planes, is vital for the security of the republic, but adequate maintenance of stand-

ards of health and alleviation of suffering are equally vital, both from a practical point of view and from that of morale. All who took part in induction-board examinations during the war realize that the maintenance and development of national health is of as vital importance as the maintenance and development of armament.

The trend of development in the facilities available for the chronically ill outlined above will not necessarily be altered by public or state medicine. With provision of public funds in any setting of public activity the question is bound to come up, "Is it worth while to spend a certain amount of effort to restore a certain type of patient?" This rationalistic point of view has insidiously crept into the motivation of medical effort, supplanting the old Hippocratic point of view. In emergency situations, military or otherwise, such grading of effort may be pardonable. But doctors must beware lest such attitudes creep into the civilian public administration of medicine entirely outside emergency situations, because once such considerations are at all admitted, the more often and the more definitely the question is going to be asked, "Is it worth while to do this or that for this type of patient?" Evidence of the existence of such an attitude stared at me from a report on the activities of a leading public hospital unit, which stated rather proudly that certain treatments were given only when they appeared promising: "Our facilities are such that a case load of 20 patients is regularly carried. . . in selecting cases for treatment careful consideration is given to the prognostic criteria, and in no instance have we instituted treatment merely to satisfy relatives or our own consciences." If only those whose treatment is worth while in terms of prognosis are to be treated, what about the other ones? The doubtful patients are the ones whose recovery appears unlikely, but frequently if treated energetically, they surprise the best prognosticators. And what shall be done during that long time lag after the disease has been called incurable and the time of death and autopsy? It is that period during which it is most difficult to find hospitals and other therapeutic organizations for the welfare and alleviation of suffering of the patient.

Under all forms of dictatorship the dictating bodies or individuals claim that all that is done is being done for the best of the people as a whole, and that for that reason they look at health merely in terms of utility, efficiency and productivity. It is natural in such a setting that eventually Hegel's principle that "what is useful is good" wins out completely. The killing center is the *reductio ad absurdum* of all health planning based only on rational principles and economy and not on humane compassion and divine law. To be sure, American physicians are still far from the point of thinking of killing centers, but they have arrived at a danger point in thinking, at which likelihood of full rehabilitation is considered a factor that should determine the amount of time, effort and cost to be devoted to a particular type of patient on the part of the social body upon which this decision rests. At this point Americans should remember that the enormity of a euthanasia movement is present in their own midst. To the psychiatrist it is obvious that this represents the eruption of unconscious aggression on the part of certain administrators alluded to above, as well as on the part of relatives who have been understandably frustrated by the tragedy of illness in its close interaction upon their own lives. The hostility of a father erupting against his feebleminded son is understandable and should be considered from the psychiatric point of view, but it certainly should not influence social thinking. The development of effective analgesics and pain-relieving operations has taken even the last rationalization away from the supporters of euthanasia.

The case, therefore, that I should like to make is that American medicine must realize where it stands in its fundamental premises. There can be no doubt that in a subtle way the Hegelian premise of "what is useful is right" has infected society, including the medical portion. Physicians must return to the older premises, which were the emotional foundation and driving force of an amazingly successful quest to increase powers of healing and which are bound to carry them still farther if they are not held down to earth by the pernicious attitudes of an overdone practical realism.

What occurred in Germany may have been the inexorable historic progression that the Greek historians have described as the law of the fall of civilizations and that Toynbee[18] has convincingly confirmed — namely, that there is a logical sequence from Kòros to Hybris to Ate, which means from surfeit to disdainful arrogance to disaster, the surfeit being increased scientific and practical accomplishments, which, however, brought about an inclination to throw away the old motivations and values by disdainful arrogant pride in practical efficiency. Moral and physical disaster is the inevitable consequence.

Fortunately, there are developments in this democratic society that counteract these trends. Notable among them are the societies of patients afflicted with various chronic diseases that have sprung up and are dedicating themselves to guidance and information for their fellow sufferers and for the support and stimulation of medical research. Among the earliest was the mental-hygiene movement, founded by a former patient with mental disease. Then came the National Foundation for Infantile Paralysis, the tuberculosis societies, the American Epilepsy League, the National Association to Control Epilepsy, the American Cancer Society, The American Heart Association, "Alcoholics Anony-

mous" and, most recently the National Multiple Sclerosis Society. All these societies, which are co-ordinated with special medical societies and which received inspiration and guidance from outstanding physicians, are having an extremely wholesome effect in introducing fresh motivating power into the ivory towers of academic medicine. It is indeed interesting and an assertion of democratic vitality that these societies are activated by and for people suffering from illnesses who, under certain dictatorships, would have been slated for euthanasia.

It is thus that these new societies have taken over one of the ancient functions of medicine — namely, to give hope to the patient and to relieve his relatives. These societies need the whole-hearted support of the medical profession. Unfortunately, this support is by no means yet unanimous. A distinguished physician, investigator and teacher at an outstanding university recently told me that he was opposed to these special societies and clinics because they had nothing to offer to the patient. It would be better to wait until someone made a discovery accidentally and then start clinics. It is my opinion, however, that one cannot wait for that. The stimulus supplied by these societies is necessary to give stimulus both to public demand and to academic medicine, which at times grows stale and unproductive even in its most outstanding centers, and whose existence did nothing to prevent the executioner from having logic on his side in Germany.

Another element of this free democratic society and enterprise that has been a stimulus to new developments is the pharmaceutical industry, which, with great vision, has invested considerable effort in the sponsorship of new research.

Dictatorships can be indeed defined as systems in which there is a prevalence of thinking in destructive rather than in ameliorative terms in dealing with social problems. The ease with which destruction of life is advocated for those considered either socially useless or socially disturbing instead of educational or ameliorative measures may be the first danger sign of loss of creative liberty in thinking, which is the hallmark of democratic society. All destructiveness ultimately leads to self-destruction; the fate of the SS and of Nazi Germany is an eloquent example. The destructive principle, once unleashed, is bound to engulf the whole personality and to occupy all its relationships. Destructive urges and destructive concepts arising therefrom cannot remain limited or focused upon one subject or several subjects alone, but must inevitably spread and be directed against one's entire surrounding world, including one's own group and ultimately the self. The ameliorative point of view maintained in relation to all others is the only real means of self-preservation.

A most important need in this country is for the development of active and alert hospital centers for the treatment of chronic illnesses. They must have active staffs similar to those of the hospitals for acute illnesses, and these hospitals must be fundamentally different from the custodial repositories for derelicts, of which there are too many in existence today. Only thus can one give the right answer to divine scrutiny: Yes, we are our brothers' keepers.

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DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX BY SPONGE BIOPSY*

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SINCE cancer in its early stage is a localized lesion, successful treatment depends on complete surgical removal of the diseased tissue or its complete destruction by adequate radiation. The diagnosis of cancer by the recognition and proper interpretation of early clinical signs and symptoms is in several important categories wholly inadequate, as witnessed by the poor results in the treatment of gastric and bronchogenic carcinoma. In lesions of the stomach and lung the symptoms appear and the diagnosis is made at a stage of the disease in which the cancer most often has advanced beyond the possibility of complete removal. For successful treatment in such cases, the detection of the disease will have to be made *before* the onset of clinical complaints. The cervix uteri because of its ready accessibility provides an ideal site for the detection of early carcinoma prior to the onset of signs, symptoms or anatomic changes visible on clinical inspection. Two such cases diagnosed by the method of sponge biopsy[1-3] and treated by hysterectomy are reported below.

FIGURE 1. *First Sponge Biopsy in Case 1.*
High-power photomicrograph, demonstrating irregular broad band of gelatin sponge to the left and below. In the center and below are two particles of cancer tissue made up of large cells with large, darkly staining, irregular nuclei, showing marked variation in size and shape.

METHOD

The method of sponge biopsy depends on the absorption of fluid, cells and tissue particles from the surface of an ulcer or mucous membrane rubbed by an absorbing sponge of suitable structure and chemical composition. The sponge and absorbed contents are fixed in formalin, embedded in paraffin, sectioned by microtome and stained with hematoxylin and eosin. The stained paraffin sections are then examined by a qualified pathologist for the presence of tumor cells and fragments of tumor tissue.

A suitable sponge must be of such chemical composition as to withstand the solvent action of alchohol, chloroform, acetone or other fluids used in tissue preparation. For this purpose we have worked mostly with gelfoam No. 12 (Upjohn). A flat square of sponge 2.0 by 2.0 by 0.5 cm. is clamped along one margin by a surgical sponge forceps. The ulcer is wiped clean with dry sterile gauze, and then the dry diagnostic sponge is rubbed gently over the suspected area. After the sponge becomes wet, it is pressed more firmly between the tissue and the sponge holder, with slight rubbing. Each of the two sponge surfaces is thus brought into contact with the area to be examined, to permit later sectioning from either surface after embedding in paraffin. The flat sponge is used for rubbing of the surface of the cervix uteri, or lesions of the skin, mouth, lower rectum and so forth. When working through a long tube such as a sigmoidoscope, one may employ a small piece of sponge at the end of a uterine forceps. This is also useful for insertion into the external os of the cervix uteri. In bronchoscopy, a special narrow sponge holder is chosen.

To ensure the absorption of an adequate amount of material it is best to rub the sponge around the edge of the ulcer near the surrounding normal tissue. Also, the outside surface of the metal ring of the sponge holder may be filed to produce several radial grooves. These will help to dislodge tiny particles from the ulcer.

The method depends for its success in the first place on the actual transfer of cancerous tissue from the lesion to the sponge, secondly, on the proper preparation of sections and, thirdly, on the recognition of cancerous material in the slide during

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microscopical examination by the pathologist. The first step depends on the physician. He must be able to see the lesion clearly (this often is not easy at the far end of a bronchoscope or sigmoidoscope). On the other hand, since early carcinoma of the cervix may present no visible changes, one must rub the sponge over the area in which these lesions begin, the ring of the external os, the adjacent portion of the lips of the cervix and the adjacent lower cervical canal. When a visible lesion presents a grayish-white necrotic base, the dead tissue must be removed by gauze before the diagnostic sponge is applied. The success of the method depends more than anything else upon the ability to reach the lesion, and to rub the sponge firmly over it. The technician should embed the sponge so as to cut sections from the flat surface, usually discolored after having been rubbed over the ulcer. If tiny particles of tissue are seen in the formalin bottle, they should be processed along with the sponge, and placed in contact with the sponge surface to be cut, before embedding. One may accomplish this by placing the tissue particles in the melted paraffin and then covering them with the sponge. The sections taken from the immediate surface of the paraffin block should be mounted. Deeper sections may also be taken. The pathologist can quickly familiarize himself with the findings in sponge biopsy by rubbing sponges over fresh tumors immediately after removal from the patient. Sections from such sponges will show the ease with which cancerous material may be absorbed by a suitable sponge and demonstrated on microscopical examination.

FIGURE 2. *Second Sponge Biopsy in Case 1.*
High-power photomicrograph, showing one of the particles of cancer tissue embedded in the sponge. The gelatin sponge is seen to the left. The tumor-cell nuclei are large and darkly staining, with marked variation in size and shape.

CASE REPORTS

CASE 1. C. J. (8125–48), a 40-year-old married woman, reported to the New York Polyclinic Outpatient Department on May 24, 1948, complaining of backache of 2 years' duration.

The patient had 2 children, 13 and 16 years of age. The past history showed pneumonia in 1926. The menstrual periods were regular, occurring every 28 days and lasting for 4 days. No irregularities in menstrual bleeding, no dysmenorrhea and no spotting had been noticed.

Physical examination disclosed a slightly overweight, well developed woman. Examination of the head, neck, chest and abdomen revealed no abnormalities. On pelvic examination a Bartholin-gland cyst, left side, and a retroverted uterus were found. The cervix uteri on direct visual inspection through a bivalve speculum appeared normal.

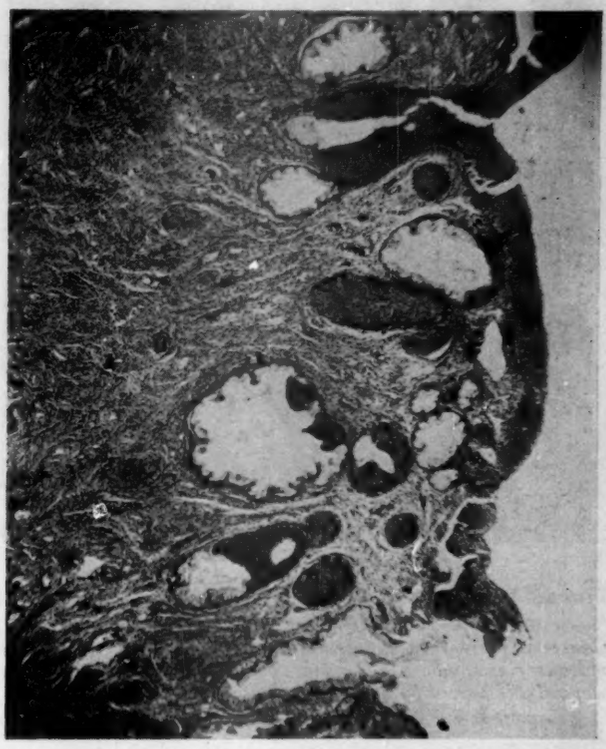

FIGURE 3. *Surgical Specimen in Case 1 (Low-Power Photomicrograph of the Cervix).*
The plane of the section is perpendicular to the axis of the cervical canal just above the external os. Note the thick layer of darkly staining cells, with finger-like projections into the underlying tissue. Filling, destruction and replacement of mucous glands by the advancing growth are seen.

The temperature was 99.2°F., the pulse 80, and the respirations 20. The blood pressure was 148/80.

Examination of the blood showed a red-cell count of 4,730,000, with a hemoglobin of 90 per cent (Sahli). The sedimentation rate was 5 mm. in 1 hour. The urine was clear, with a negative test for sugar and a faint trace of albumin.

Microscopical examination of the sediment demonstrated an occasional white cell and red cell, with no casts. A cervical smear was negative for gonococci.

On October 14 a sponge biopsy was performed by rubbing of a flat piece of sponge over the cervix uteri visualized through the speculum. A longitudinal piece of sponge held at the end of a uterine clamp was inserted into the cervical canal. The sponges were treated and examined in the manner described above. The report of the sponge biopsy was as follows:

> Microscopical examination of the sponge from the cervical canal shows clumps of large atypical epithelial tumor cells. A small particle of tissue (Fig. 1) is made up of large, darkly staining epithelial cells, with large nuclei, showing marked atypism and variations in size and shape.

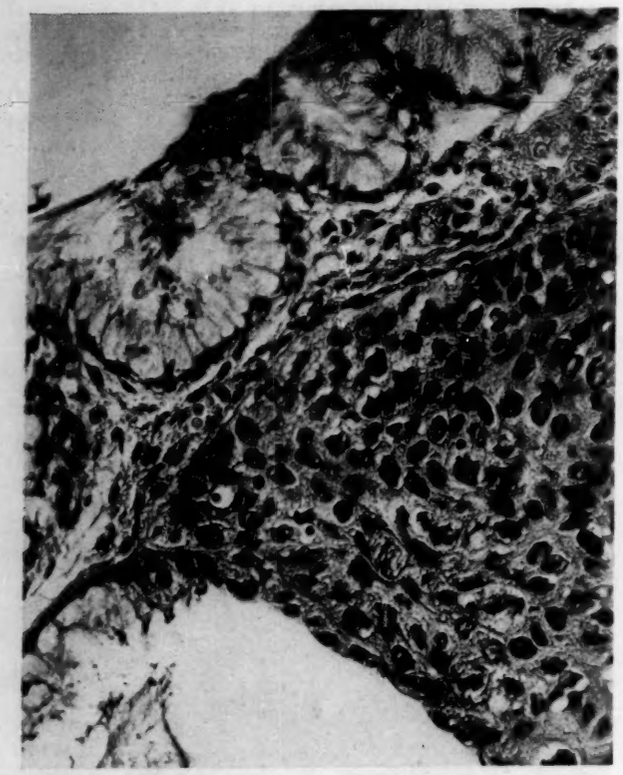

FIGURE 4. *Surgical Specimen in Case 1 (High-Power Photomicrograph).*

Cancer is present in the center and to the right, with intact, mucous glands above. The mucous gland below and to the left is partly destroyed by advancing tumor.

> The large sponge rubbed over both lips of the cervix and external os shows abundant stratified squamous epithelium, as well as tiny particles of cancer tissue and individual cancer cells.

The sponge biopsy was repeated on October 28, and showed fragments of cancer tissue (Fig. 2) in the sponge inserted into the cervical canal; scattered cancer cells were found in the sponge rubbed over the lips and external os of the cervix.

On the basis of the sponge biopsy, a diagnosis of epidermoid carcinoma of the cervical canal was made, and a total hysterectomy and bilateral salpingo-oöphorectomy were performed on November 6.

Pathological examination of the specimens revealed small ovarian cysts, the largest 2 cm. in diameter. The tubes measured 8.0 x 0.6 cm. and showed several serosal cysts. The uterus appeared normal in shape and measured 10 by 6 by 5 cm. The uterine wall varied from 1.5 to 2.5 cm. in thickness. The mucosa of the cervical canal was thickened near the external os up to about 4.0 mm. A small ulcer, 3 mm. in diameter, was seen in this area. On cross section within the thickened mucosa, several pin-point, reddish spots were visible.

Microscopical examination was reported as follows:

> There is moderate hyperplasia of the endometrial glands, with dilatation and cyst formation. The mucosa of the cervical canal is covered by a layer of closely packed, darkly staining cells (Fig. 3), rather large, showing considerable variation in size and shape. The nuclei are also large and reveal occasional mitotic figures. At several points finger-like projections of this tissue extend into the underlying fibromuscular tissue and into the underlying mucous glands, several of which are partly destroyed and replaced by the invading growth (Fig. 4). Also present are several dilated and cystic mucous glands. The epithelial surface covering the external os is intact. Beneath it are several mucous cysts. The diagnosis is epidermoid carcinoma of the cervix in situ.

CASE 1. D. S., a 48-year-old woman whose vague complaints were thought to be of menopausal origin, was accordingly referred to a gynecologist for possible endocrine therapy. In the course of pelvic examination a sponge biopsy of the cervix uteri was performed. There were no visible abnormalities of the external os or lips of the cervix on direct inspection. There were no abnormalities of menstruation, no abnormal bleeding and no spotting. The findings on sponge biopsy were reported as follows:

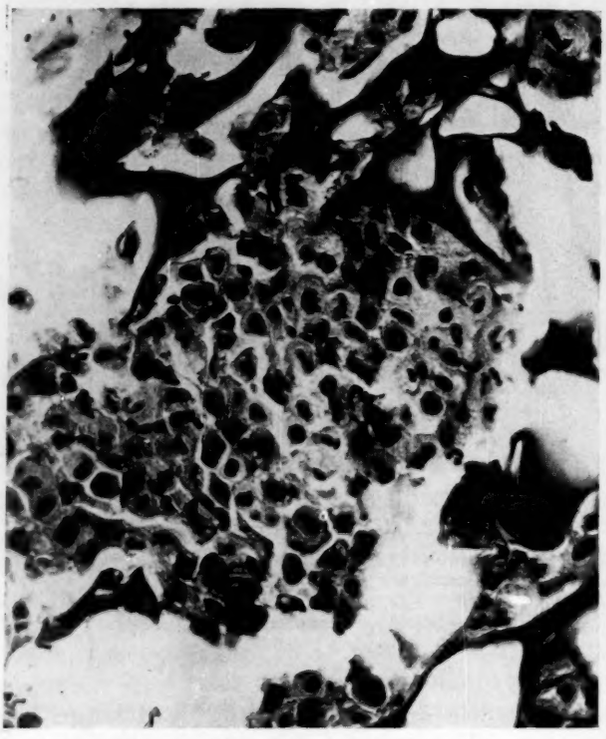

FIGURE 5. *Sponge Biopsy in Case 2.*

High-power photomicrograph, showing a particle of cancer tissue embedded in the sponge. The cell nuclei are large and darkly staining, with marked variation in size and shape.

> Microscopical examination discloses many large, darkly staining, atypical cells, with large nuclei showing marked variations in size and shape. Some cells have double nuclei. Small particles of tissue made up of atypical cells are also present (Fig. 5). There is a moderate amount of blood. The findings are those of epidermoid carcinoma of the cervix. Confirmation by surgical biopsy is advisable prior to treatment.

About 2 weeks later surgical biopsy in the form of curettings from the external os was done. The pathologist's report was as follows:

The specimen consists of several small fragments of soft red and brown tissue aggregating in all about 0.2 cc. Microscopical examination shows hyperplasia of large undifferentiated epithelial cells in thick layers. The tissue appears coagulated. There is a tendency to concentric formations. Groups of cells that stain more clearly demonstrate large nuclei, darkly staining, with considerable variation in size and shape. The basement membrane is indistinct and in part is traversed by the growing cells. The diagnosis is epidermoid carcinoma of the cervix.

A month after the cervical os was curetted, a complete hysterectomy with bilateral salpingo-oöphorectomy was performed. The pathological report was as follows:

The specimen consists of a uterus with both tubes and ovaries attached. The cervix has been incised along the posterior wall. The specimen is fixed in formalin. The uterus measures 9 by 6 by 5 cm. On section the uterine wall measures 2 cm. in thickness. The endometrium measures about 3 mm. The lips of the cervix are reddish brown. The surface is somewhat irregular, and the external os has a granular appearance. The cervical canal is pale gray. The endometrium is reddish brown. On the lip of the cervix between the os and the circumference, in the lower right-hand quadrant, there is an ulcerated grayish-brown area, 7 mm. in diameter. On section the underlying tissue shows the extension of pearly white tissue from the surface, reaching about 5 to 8 mm. into the depths. The ovaries feel somewhat firm and measure 2.5 to 3.0 cm. in length.

Microscopical examination of the ulcerated area of the cervical lip described in the gross shows an abundant growth of large, atypical tumor cells, epidermoid in type, extending in cords and irregular masses into the underlying muscular tissue (Fig. 6). There is considerable necrosis, fibrosis and lymphocytic infiltration between and around the masses of tumor tissue. Surrounding the tumor growth are numerous dilated, thin-walled blood vessels. Between the ulcer and the cervical os the epithelial zone is thickened and made up of large vesicular, anaplastic cells, many containing large nuclei and distinct nucleoli. Irregular masses of invasive tumor tissue are also seen in the area of the external os. The abnormal epithelial growth extends also in the opposite direction over the cervical lip, and at one point makes an abrupt transition to normal epithelium. The latter shows the oblique line often described. In cut sections the hyperplastic surface growth extends down into the mucous glands, filling, destroying and replacing them. The individual cells are markedly atypical. The endometrial glands show slight hyperplasia. The myometrium appears normal. In the ovary there are several corpora albicantia and considerable hyperemia. The diagnosis is epidermoid carcinoma of the cervix.

Review of this case indicated that the tissue obtained by surgical biopsy consisted of anaplastic superficial growth. The more differentiated and more characteristic epidermoid type of cancer tissue was confined to the invasive area on the lip. This area was not detectable on clinical inspection. It was missed on surgical biopsy. Sponge biopsy, however, gathered from its surface characteristic cells and tissue particles.

Discussion

Of the 2 cases of cancer of the cervix reported the first was superficial or intraepithelial. The second was similar except that in one area a small invasive tumor mass, 0.8 cm. in greatest diameter, had developed. The incidence of early, superficial or intraepithelial cancer of the cervix varies somewhat according to the specimens or patients studied, and the methods used for obtaining material for biopsy. In a study of 1200 whole cervices, most of which were from patients on whom hysterectomies had been performed, Pund and Auerbach[4] observed 47 cases of preinvasive carcinoma (almost 4 per cent). TeLinde and Galvin,[5] by the use of surgical biopsy, found 8 early cancers in 704 cases. Foote and Stewart[6] reported the collection of 27 pathological specimens of intraepithelial carcinoma of the cervix in the Memorial Hospital laboratory during a period of three years. The three reports mentioned demonstrate the frequency of these lesions and indicate the importance of detecting them. Foote and Stewart, by serial sections, demonstrated the precise location of these lesions at the cervical os, cervical canal and cervical lips. These areas are readily accessible to the diagnostic sponge for the collection of tissue for microscopic examination.

Figure 6. *Case 2. Surgical Specimen from Cervix Uteri. A very low-power photomicrograph, showing invasiveness of cancer with destruction of underlying tissue.*

Summary

Two cases of early asymptomatic carcinoma of the cervix diagnosed by sponge biopsy are reported. The first case was superficial and intraepithelial. The second was similar but included one invasive area 0.8 cm. in greatest diameter. The frequency

of these lesions varied from 1 to 4 per cent in the series cited.

A cervix that looks normal on clinical visual inspection may be the site of early cancer. The two cases reported indicate the usefulness of sponge biopsy in obtaining tissue for microscopical examination in the diagnosis of early carcinoma of the cervix.

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DIHYDROSTREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS*

With Particular Reference to Its Toxicity As Compared with That of Streptomycin

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SINCE September 1946 the United States Veterans Administration Hospital, Rutland Heights, Massachusetts, a 600-bed hospital for the treatment of veterans with tuberculosis, has been engaged in the study of streptomycin and its effect in controlling various forms of the disease. It is not within the province of this paper to discuss the results of these studies, which have been presented in previous reports.[1-6] In most cases streptomycin has not been considered to be definitive therapy, but rather a very helpful adjunct to other well established methods of treatment, such as bed rest and the various forms of collapse therapy, in the pulmonary cases, and bed rest alone, or in conjunction with surgical procedures, in the extrapulmonary cases. The latter group includes draining sinuses and tuberculosis of the bones, joints, lymph nodes, alimentary tract, kidneys and peritoneum.

The chief deterrents to the use of streptomycin are toxicity and the rapid emergence of resistant strains of the organism concerned, the *Mycobacterium tuberculosis*. Toxicity for the most part is a neurotoxicity directed against the eighth cranial nerve, particularly its vestibular branch, so that vestibular function is either impaired or lost. Important, but less so than the neurotoxic tendency of the drug, is the allergic reaction, whose chief manifestation is skin eruption. Much of the fear of toxicity has been allayed by shortening of the course of the drug and lessening of the daily dosage. Resistance of the tubercle bacillus to streptomycin is far from remedied and remains the bug-a-boo of the drug's true effectiveness.

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The dihydrostreptomycin used in this study was furnished by Merck and Company, Rahway, New Jersey.

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To combat the toxicity, Merck and Squibb chemists have been working on various modifications of the original streptomycin with the result that there has emerged a closely related compound produced from crude streptomycin complex by hydrogenation, which has been called dihydrostreptomycin.

We have treated 20 patients with this new compound for ninety days.

The principal object of the study was to determine the toxicity of the drug, although its therapeutic properties have not been overlooked.

Following the modus operandi of all streptomycin studies carried out in Veterans Administration Hospitals, more carefully to anticipate and evaluate toxicity from the drug, numerous laboratory tests were carried out before treatment and at weekly intervals thereafter, unless otherwise specified. These procedures consisted of audiograms (done bi-weekly), caloric tests using ice water (done bi-weekly), urine analyses, complete blood counts, erythrocyte sedimentation rates (Cutler method), urea clearance, blood urea nitrogen, prothrombin times, stereoroentgenograms of the chest (monthly) and sputum concentrates for acid-fast bacilli (monthly). In addition to these tests, sensitivity studies were carried out and dihydrostreptomycin blood levels determined.

Preparation for Injection

The drug was received in 1-gm. vials, and the material, a white powder, made a colorless clear solution; 4 cc. of sterile distilled water was added to the vial, and 2 cc., equivalent to 0.5 gm. of the drug, was injected at a dose, usually in the gluteal muscles. In the first few weeks of treatment, injections were given every four hours "around the clock" to the patients receiving 3 gm., and every four hours from 8 a.m. through 8 p.m. to those receiving 2 gm. daily.

The first lots of the drug caused considerable irritating reaction at the site of injection. In addition, there were paresthesias in 6 patients manifested by numbness of the lips. When the study was about half completed, Dr. James Carlisle, medical director of the Merck Company, who had followed our work with interest, sent us some dihydrostreptomycin sulfate for trial, stating that it had been found less irritating in animals than the hydrochloride. We injected 0.5 gm. of the sulfate in the left arms of the 20 patients and at the same time injected 0.5 gm. of the hydrochloride in the right arms, without informing the patients of our experiment. With one exception all patients had pain, burning or soreness in the right arm, and none in the left. The exception had pain in neither arm. We were then convinced that the dihydrostreptomycin hydrochloride was much more irritating than the dihydrostreptomycin sulfate, and since then we have used the sulfate when it was obtainable. Later in the study, injections were given as follows: for the patients receiving 3 gm., 0.5 gm. in each buttock three times a day; for those receiving 2 gm., 0.5 gm. in each buttock twice a day, because injection of 1 gm. at one site appeared to be too irritating.

Cases Treated

Twenty patients with active pulmonary tuberculosis, including 1 with generalized miliary tuberculosis, were treated for ninety days. Half these received 2 gm. of dihydrostreptomycin daily, and half 3 gm. daily. The extent of the disease was advanced in all cases according to the classification of the National Tuberculosis Association; 18 were far advanced, 1 was moderately advanced, and 1 had generalized miliary tuberculosis. Fourteen patients (70 per cent) had cavitary disease; 17 (85 per cent) had bilateral lung involvement; and 6 (30 per cent) had more than 50 per cent exudative disease as determined by roentgenograms. Nineteen patients had positive sputums. We were able to obtain positive cultures in 18 of these. The clinical and roentgenographic indication of a generalized miliary tuberculosis was so profound in 1 patient that treatment was given in spite of negative sputum smears and cultures. Subsequent events in this case confirmed our impression that the hematogenous infection was of tuberculous origin; tuberculous meningitis developed soon after completion of the course, the patient died, and autopsy confirmed the diagnosis. All but 1 of the patients were white men, the exception being a Negro forty-two years of age. The ages ranged from twenty-one to fifty-three, the majority being in the third and fourth decades.

Toxicity

Subjective Symptoms

During the first week of treatment, aside from the tissue irritation, 6 patients complained of paresthesias, for the most part involving the lips, which were described as "numbness," "feeling of fullness" and "dead sensation" by various patients. One of these patients likewise complained of paresthesias involving the tip of the left thumb, index and middle finger, of forty-eight hours' duration. These paresthesias appeared within the first two days of treatment. They were of short duration in all cases, lasting from five minutes to forty-eight hours. The drug was not discontinued because of them. The paresthesias, having disappeared, did not return. At first it was believed they were manifestations of the neurotoxicity of dihydrostreptomycin. However, since they did not appear in any of the patients who subsequently received other lots of the drug, which presumably had been more purified, it is now believed that these early toxic manifestations were not due to the drug itself but to impurities in the early lots administered.

Two patients complained of gastrointestinal upsets during the course of treatment: 1 of nausea on the morning following institution of treatment, and the other of nausea, vomiting, chills and fever for two days during the third week of treatment. Whether the disturbance was an effect of the drug cannot be stated with certainty, since it may have been caused by a gastrointestinal infection unrelated to treatment.

Between the thirtieth and the forty-seventh day of treatment, 4 patients complained of tinnitus that was of transient duration but recurrent in two patients. This was not accompanied by impairment of hearing or audiometric changes of significant degree in any of the patients, so that the drug was not discontinued because of this symptom. One patient complained of slight dizziness and stated that he walked as though he had "blind staggers." This symptom appeared at the end of the fifth week of treatment. Actually the patient demonstrated little ataxia when he was observed getting out of bed and walking across the room. At that time, caloric tests were normal. On the sixtieth day of treatment, however, ataxia was definite, and the caloric test revealed almost complete loss of vestibular function. This patient received 3 gm. of the drug daily. The drug was immediately stopped. No patients demonstrated clinical hypersensitivity to the drug as evidenced by skin eruptions, edema of the eyelids, bronchospasm or arthralgia. There were no cases of agranulocytosis or purpura.

Laboratory Evidence of Toxicity

Six patients (30 per cent) of the group of 20 showed eosinophil counts above 5 per cent. The counts were never higher than 8 per cent and usually appeared in the third and fourth weeks of treatment, returning to normal by the eighth week.

Evidence of renal impairment. Urinalyses were essentially normal in all but 2 cases. One of these patients had a single specimen that showed

many hyaline casts after two weeks of therapy; subsequent specimens were negative. Urine from the other patient showed many white cells and granular casts after four weeks and nine weeks of treatment. This patient's most recent urea clearance has shown a decided drop to 38 per cent; he is fifty-three years of age and has far advanced tuberculosis. Further studies to rule out renal tuberculosis are being performed. Blood urea nitrogen determinations have been normal.

Urea clearance tests showed no significant reduction except in the one case cited above. Blood urea nitrogen determinations were within normal limits in all cases.

There was no clinical evidence of liver damage in any of the patients, although tests of liver function were not carried out, except for a study of weekly prothrombin times in all cases. Prothrombin-time measurements varied through the weeks in most patients, but at no time showed any significantly marked rise or fall from the normal.

Hematologic evidence of toxicity. Red-cell counts were unchanged from pretreatment levels in 11 patients (55 per cent).

Because of the human element of error in counting red blood cells, we considered only deviations of 1,000,000 or more red cells to be significant; 45 per cent showed a drop of 1,000,000 cells after the first week of treatment. All these counts returned to their pretreatment level between the eighth and the twelfth week of treatment.

The photoelectric colorimeter was used for determinations of hemoglobin. Deviations of 5 per cent or more were recorded. Except for 3 patients, who demonstrated a slight fall in hemoglobin soon after treatment started, the determinations in the remaining patients either showed no significant deviation from pretreatment levels or became higher during the early weeks of treatment.

There was considerable variation in the white-cell and differential counts, but in no case was there a definite leukopenia or agranulocytopenia.

Erythrocyte sedimentation rates (Cutler method). Changes of 5 mm. or more from pretreatment readings were recorded. Five patients (25 per cent) demonstrated a fall to normal during the fifth to the tenth week of treatment. Eight (40 per cent) patients demonstrated a fall from pretreatment readings, but not to normal, between the fifth and the twelfth week of treatment. Seven patients demonstrated no change in their sedimentation rates during treatment. Six of these were elevated, and 1 was normal.

Caloric Tests

Bi-weekly caloric tests were carried out, a modified Kobrak technic, injecting 5 cc. of ice water in each ear, being used and the time of appearance of nystagmus and its duration being noted. During the ninety-day course only 1 patient of the entire group showed any substantial loss in vestibular function.

Audiometric Tests

Bi-weekly audiograms were made on all patients. Only 1 patient revealed any impairment of cochlear-nerve function audiometrically during treatment, and this was slight. There was no clinical deafness.

Clinical Observations

In marked contrast to the feeling of well-being and increased appetite, which was striking in the great majority of patients treated with streptomycin, the present group of patients receiving dihydrostreptomycin experienced little benefit in this respect. In fact several patients complained of loss of appetite during the first few weeks of treatment. Euphoria in the group was conspicuous by its absence.

A gain in weight during treatment was observed in 15 patients (75 per cent). The weight of 1 patient remained stationary, and 4 patients (20 per cent) lost 3 pounds or less. Of those who gained, 4, or 20 per cent, showed a gain from 1 to 5 pounds, 3, or 15 per cent, gained from 5 to 10 pounds, and 8, or 40 per cent, gained over 10 pounds.

Seven patients were afebrile at the onset of dihydrostreptomycin therapy, and these patients continued afebrile throughout treatment. Of the 13 patients with fever, 7 reverted to normal, 1 after three days of therapy, 3 after three weeks of therapy, and the remainder in six to twelve weeks.

Eight patients showed pulse rates below 90 before treatment, and these rates did not change. One patient, whose rate ranged between 90 and 100 before treatment, maintained approximately the same slightly elevated rate. Eleven patients had rates persistently above 100 prior to treatment with the drug; 5 of these continued to have rates above 100 but lower than the pretreatment rates; in the other 6 the pulse rates were reduced to 90 or below. (All pulse rates recorded are the patient's usual late afternoon rates taken while he was on complete bed rest.)

Although cough and expectoration were not uniformly severe in this group, all patients showed moderate to marked reduction in the severity of the cough and lessened expectoration.

Nineteen patients had positive sputums prior to the institution of therapy. The twentieth patient was the case of generalized miliary tuberculosis described above. Three patients had sputums that were negative after two weeks to one month of dihydrostreptomycin therapy and were still negative at the completion of their course. In the other 16 the specimens were considered to be positive.

The roentgenograms of the patient with miliary tuberculosis cleared almost completely during treatment, but after completion of his course of therapy,

tuberculous meningitis developed and was confirmed by post-mortem examination.

Roentgenographic Observations

At the completion of the ninety-day course of the drug, 12 patients (60 per cent) showed improvement by x-ray study; however, half these cases showed only slight or minimal improvement. Seven patients (35 per cent) demonstrated no change on x-ray examination, and 1 patient (5 per cent) appeared worse.

Of the 12 patients whose x-ray films revealed improvement, 8 showed improvement after one month, 3 after two months, and 1 at the completion of treatment.

Blood Levels and Sensitivity Studies

Concentration of Dihydrostreptomycin in Blood Serum

Dihydrostreptomycin blood levels were determined by the tube dilution method, *Staphylococcus aureus* (SM) being used as the test organism. Blood-level determinations were carried out on only 6 patients. A single determination was done on each patient. Blood for the tests was drawn within an hour of the administration of dihydrostreptomycin. At the time these tests were carried out, patients were being given single intramuscular injections of 1 gm. twice daily, or three times daily, depending upon the regimen followed for their particular group.

The average one-hour blood level for a group of 3 patients receiving 3 gm. of dihydrostreptomycin daily (three divided doses of 1 gm. each) was found to be 42.6 microgm. per cubic centimeter. The average one-hour blood level for a group of 3 patients receiving 2 gm. of dihydrostreptomycin daily (two divided doses of 1 gm. each) was found to be 20.7 microgm. per cubic centimeter.

Determination of Dihydrostreptomycin Sensitivity of Tubercle Bacilli

Routine sensitivity determinations were performed with the use of a Dubos liquid medium containing varying concentrations of dihydrostreptomycin. Tubes with dihydrostreptomycin, as well as suitable controls, were inoculated with standard suspensions of five-day-old cultures of tubercle bacilli in a Dubos medium prepared from primary cultures grown on potato-egg-glycerin slants. Inoculated tubes were incubated at 37°C. Development of turbidity, indicating active growth of the tubercle bacilli, often could be noted within one or two days. A Coleman model 6 junior clinical spectrophotometer, measuring transmission of light at a wave length of 620 millimicrons, was used in these determinations. Final readings were not made before the fourteenth day of incubation, however.

To supplement the routine procedure described above, sensitivity determinations on recent specimens have been carried out with a modified Herrold egg-yolk-agar solid medium with malachite green[7] containing varying concentrations of dihydrostreptomycin. Utilization of this medium permits results of sensitivity determinations to be placed on a quantitative, as well as a qualitative, basis, since the ratio of resistant to sensitive tubercle bacilli in a given inoculum can be estimated readily by comparison of the amounts of growth in test cultures with that of the control culture.

Complete data on sensitivity tests for all twenty patients in this series are not available, since cultural studies on recently submitted specimens are still in progress.

As was expected, pretreatment cultures of tubercle bacilli obtained from 18 of the 20 patients were found to be sensitive to 1 microgm. per cubic centimeter of dihydrostreptomycin. It has not been found possible thus far to demonstrate tubercle bacilli by cultural methods in sputum specimens obtained from the other 2 patients, 1 of whom was being included in the group that received 3 gm. of dihydrostreptomycin daily, and the other in the group that received 2 gm. daily.

Sufficient data have been accumulated to show that 4 patients of the 10 who received 3 gm. of dihydrostreptomycin daily produced tubercle bacilli resistant to 100 (or more) microgm. per cubic centimeter of dihydrostreptomycin within the first thirty to fifty days of therapy. One patient of the 10 who received 2 gm. daily also demonstrated resistant tubercle bacilli. This was noted on the ninety-fourth day following institution of therapy and represented cultural data obtained from a post-treatment specimen. It is not possible to estimate more closely at what time resistance to dihydrostreptomycin developed since, inadvertently, no other specimens were submitted to the laboratory prior to the end of therapy.

By use of the modified Herrold medium, it was found that in each case in which resistance to dihydrostreptomycin had developed, 75 to 100 per cent of the culturally recoverable tubercle bacilli present in corresponding sputum specimens were resistant to at least 100 microgm. per cubic centimeter of dihydrostreptomycin.

The sputum of a patient who received 3 gm. of dihydrostreptomycin daily was positive by culture six weeks after termination of therapy. The culture proved sensitive to less than 1 microgm. per cubic centimeter of dihydrostreptomycin. Incomplete studies on 2 other patients of this series show that 1 patient's culture was sensitive at the thirty-eighth day, and the other on the seventy-second day of treatment. Incomplete studies on 4 patients who received 2 gm. daily show that cultures were still sensitive at the end of eighty-five, eighty-three, sixty-three and fifty-three days of treatment, respectively. No post-treatment data for this group are available.

Supported by the data presented above there appears to be a trend showing that the resistance to dihydrostreptomycin develops in direct proportion to the size of the dosage used in therapy.

Though no final conclusions can be reached on the basis of the foregoing partially complete studies, it seems probable that the regimen consisting of intramuscular administration of 3 gm. of dihydrostreptomycin daily for a period of ninety days will result in a higher percentage of cases resistant to dihydrostreptomycin than a similar regimen of 2 gm. daily.

Discussion

Nineteen patients with pulmonary tuberculosis and 1 with generalized miliary tuberculosis have been treated with dihydrostreptomycin. Ten patients received 2 gm. of the drug daily, and 10 received 3 gm. daily, for a period of ninety days. It was the main purpose of our study to evaluate any toxicity that the drug might possess in the dosage given. Accordingly, numerous laboratory tests were carried out at regular intervals, for the most part at weekly intervals. We also evaluated subjective symptoms and signs indicative of toxicity. The early symptoms of paresthesias in 6 patients, at first thought to be evidences of neurotoxicity of the drug, now appear to be evidences of impurities in the first lots of drug administered, since subsequent lots failed to produce these symptoms. Tinnitus, which developed in 4 patients, may well have been a true neurotoxic manifestation, since this symptom appeared later in the course of treatment. Audiometric observations were little changed from pretreatment readings. The nausea reported in 2 patients was an early symptom and may or may not have been significant. It does not appear to be a characteristic toxic manifestation of either dihydrostreptomycin or streptomycin. Since 1 patient receiving 3 gm. daily practically lost vestibular function, and had to be dropped from the course on the sixtieth day, this demonstrates the possibility of specific toxic effects on the vestibular nerve.

Compared with streptomycin in similar dosage, vestibular-nerve toxicity appears considerably less in this group receiving dihydrostreptomycin. In our previous studies with streptomycin, of our original group of 20 patients receiving 1.8 gm. for a hundred and twenty days, 75 per cent lost vestibular function by the end of the course, and most of these had lost function by the end of sixty days. In our subsequent group of 31 patients who received 2 gm. of streptomycin for sixty days, 64 per cent completely lost vestibular function.

Eosinophilia, which was common in our series of patients receiving various dosages of streptomycin, occurred with much less frequency in the present group of dihydrostreptomycin-treated patients. For example, 30 per cent of the latter showed eosinophil counts from 5 to 8 per cent, whereas 75 per cent of the former had counts that reached an upper limit of 17 per cent. This is consistent with the lessened toxicity observed in the present study.

Renal damage has not been observed in our study, and no evidence of renal irritation has been noted except in 1 case, in contrast to 40 to 50 per cent who received 1.8 gm. of streptomycin and showed frequent albuminuria and cylindruria — not in themselves evidences of renal damage but certainly of probable renal irritation.

There has been no lasting effect of the drug on the hematopoietic system.

Prothrombin times were not altered significantly during treatment. No other liver-function tests were done, but no patient appeared to develop clinical evidence of liver damage.

Improvement was manifested by weight gain, lessened cough and expectoration, and disappearance of fever in all patients.

True evaluation of conversion of sputum cannot be made in this series since the time of observation is too short. At least three months of negative sputum should be required before one can consider a conversion definite.

Erythrocyte sedimentation rates were significantly lowered in 65 per cent of the group during treatment. This incidence is scarcely different from the decreases in the sedimentation rates that occurred in 75 per cent of 20 patients who received 1.8 gm. streptomycin for a hundred and twenty days.

Roentgenographic improvement was observed in 60 per cent, and half of these patients showed only slight or minimal improvement. This is in contrast with the first group receiving 1.8 gm. of streptomycin for a hundred and twenty days, who showed roentgenographic improvement at the end of ninety days of treatment in 75 per cent. In a series of 31 patients receiving 2 gm. of streptomycin for sixty days, 90 per cent showed improvement. In a group of 13 patients receiving 1 gm. of streptomycin for a hundred and twenty days, 84 per cent showed improvement by roentgenograms.

Therefore, not only the incidence of improvement but also the degree of improvement in the individual cases appeared less with dihydrostreptomycin.

Conclusions

From the observations in this group of 20 patients treated with intramuscular injections of 2 and 3 gm. of dihydrostreptomycin daily for ninety days, it is concluded that, in this dosage, the drug is less toxic than streptomycin in similar dosage.

The 2 patients showing the more serious evidences of toxicity, loss of vestibular function in 1 and renal irritation in the other, received 3 gm. of the drug daily.

Our observations indicate that dihydrostreptomycin in the dosage given may be less effective therapeutically than streptomycin given in similar or smaller dosage.

Resistance studies are completed and available on only 12 patients in the group at this writing, 5 of whom developed resistant organisms during treatment.

Addendum.[7] Because of the development of cochlear-nerve damage in 4 of the 20 cases reported subsequent to completion of the course of therapy, a brief description of the development of symptoms is important.

Follow-up study on the patient with ataxia on the sixtieth day of treatment, described above, reveals that he has no residual dizziness or ataxia, but vestibular function, as interpreted by the caloric test, has not returned. One week after discontinuation of therapy, tinnitus developed, and this has become slowly more marked. This patient's audiogram was not quite so good after sixty days of therapy as it was before treatment, and it has become slightly worse, though progressively so, for five months.

The second patient, a fifty-two-year-old man, received 2.0 gm. of dihydrostreptomycin daily for ninety days. One month after completion of his course of treatment he complained of moderate tinnitus, which has remained unchanged to the present (three months after treatment). Concomitantly he complained of occasional staggering, and loss of balance when bending over, these symptoms being exaggerated in the dark. No deafness was noted, but at the onset of tinnitus slight impairment of hearing was shown by the audiogram.

The third patient, a thirty-year-old man, received 3.0 gm. of dihydrostreptomycin daily for a period of ninety days. There was no evidence of cochlear-nerve involvement until two months after treatment, and since then he has had occasional tinnitus and some clinical impairment of hearing. His audiogram also showed some impairment of function at the time tinnitus developed.

The fourth patient, a thirty-seven-year-old man, received 3.0 gm. of dihydrostreptomycin daily for ninety days. One month after treatment marked tinnitus and mild deafness developed, both of which increased markedly in severity for the following month. An audiogram taken at the onset of tinnitus showed impairment of function. The audiogram taken a month later showed increased impairment.

In addition to these cases, a patient came to us after receiving dihydrostreptomycin for about two months in another hospital. Because he had miliary disease, we decided to continue antibiotic therapy but changed to 2.0 gm. of streptomycin daily. About a month after admission to this hospital (a month after dihydrostreptomycin had been stopped), he began to complain of deafness, and during the next month he became almost totally deaf.

We must add therefore to our discussion and conclusions, that in this admittedly small series of 20 cases, 4, or 20 per cent, suffered cochlear-nerve damage, which became apparent only after dihydrostreptomycin therapy was completed. In 3 of these cases nerve damage was not apparent until at least a month after completion of treatment.

Though streptomycin is a definite toxin to the eighth nerve, it more specifically attacks the vestibular branch, and much less often the cochlear division. Dihydrostreptomycin, on the other hand, appears to attack the cochlear division as frequently as the vestibular division of the eighth nerve, and much more often than streptomycin does.

We therefore believe that dihydrostreptomycin, in the dosage used at this hospital, is not the innocuous drug that we hoped it would be.

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FRACTURES OF THE DISTAL END OF THE RADIUS COMPLICATED BY FRACTURES OF THE CARPAL SCAPHOID

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THERE is a teaching that a fall on the outstretched hand may cause either a Colles fracture or a fractured carpal scaphoid, the latter usually occurring in young adults and the former in older people.[1, 2] Most of the literature ignores the possibility of both simultaneously. Our recent experience shows that the combination of the two fractures is a difficult problem that occurs in a significant number of cases and through a wide age range. Scudder,[3] Brittain,[4] Key,[5] Cleveland[6] and other authors have stated that fractures of the distal end of the radius and of the carpal scaphoid can occur simultaneously at the same injury. Most of these authorities have considered the combination rare, and none discuss its frequency or its treatment. The mechanism of both injuries is nearly always the same — a fall on the outstretched hand. Force against the scaphoid and radius is indirectly applied either through the first metacarpal and the greater multangular,[6] or through the second and third metacarpals and the capitate.[2] These bones may also be simultaneously fractured.[6, 7] Dickinson and Shannon,[8] reporting 257 scaphoid fractures in soldiers whose average age was twenty-eight years, found 3 associated fractures of the radial styloid and 2 fractures of the shaft of the radius (the level of the fracture unspecified). Kellam and McGoey,[9] reporting from a Canadian Army hospital, found that of 331 successive fractures of the radius and ulna, at all levels, 7 per cent of patients had carpal injuries, and that 10 per cent with injuries of the distal third of the radius had coincidental lesions of the carpus. No breakdown as to the specific carpal bone or the type of radial fracture is available, but in all probability the majority of the carpal injuries were fractures of the scaphoid.

An analysis of our wrist fractures for about six months shows that the combination is not uncommon, and that difficult problems of both diagnosis and treatment are met.

Analysis of Cases

Three hundred consecutive cases of recent fracture of the distal 5 cm. of the radius of all types were studied. These cases were seen between September, 1946, and April, 1947. Twenty of the 300 patients, or 6.6 per cent, had associated fractures of the carpus. Of these, 15, or 5 per cent, had fractures of the body (either waist or proximal pole) of the scaphoid; 2 had fractures of the triquetrum, and there were 1 each of the lunate, capitate and greater multangular.

The combination of radial and scaphoid fractures occurred over a wide age range. The youngest patient was fifteen, and the oldest, seventy-nine. The average age was forty-four and seven-tenths years. More than half the cases were in males. Ten of the 15 patients had radial fractures of the Colles type: 1 was impacted without displacement, 5 had backward tilting of the distal fragment, and 4 had comminuted "T" fractures involving the joint. Of the remaining 5, 3 had a chauffeur fracture of the radial styloid, 1 had a Barton fracture of the dorsal articulating surface, and there was 1 epiphyseal fracture with wide displacement of the distal epiphysis and a dorsal metaphyseal fragment. All these cases resulted from a fall on the outstretched hand except for the fractures of the radial styloid, which occurred from blows forcing the hand into dorsal and radial flexion. One case, similar to that of Cleveland,[6] had associated fractures of the greater multangular, the scaphoid and the radius (Colles type). Another case (Fig. 1) illustrates a different line of force, with fractures of the base of the third metacarpal, the waist of the scaphoid and a comminuted Colles fracture involving the joint. This case required four and a half months of immobilization for bony union to occur in the scaphoid.

Diagnostic Problem

It is hard enough to diagnose a fracture of the scaphoid when the radius is not broken. A case with separation of the scaphoid fragments presents no diagnostic difficulty, but the barely visible hairline, which may not develop until many days after injury, is a more serious problem. The pain and swelling of the radial fracture mask the signs and symptoms referable to the scaphoid, and the surgeon is apt to see at a glance the gross deformity of the radius without bothering to look farther for a suspicious hairline in the scaphoid. It is very easy to concentrate attention on the radius to the exclusion of the carpus in check x-ray films, in which oblique views are seldom required. A policy of taking frequent careful scaphoid series is the only program that can prevent most errors.[2, 6, 8]

Therapeutic Problem

None of the authors who discuss the occurrence of fractures of the scaphoid complicated by a comminuted Colles fracture mention the paradox of

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treatment that confronts the surgeon. Dorsiflexion with radial deviation is commonly accepted for treatment of the fractured scaphoid[2, 8, 10-12] but ulnar deviation with volar flexion of the wrist is generally required for treatment of the Colles fracture with a tendency to slip after reduction. Any attempt to compromise may be unfortunate, nonunion of the scaphoid and malunion of the radius being equally undesirable. Fortunately, this dilemma is not always encountered. A chauffeur fracture associated with scaphoid fractures may be treated for the scaphoid alone, especially since dorsal and radial flexion of the wrist relaxes the brachioradialis pull, preventing displacement of the radial styloid. Some Colles fractures and nearly all epiphyseal fractures of the distal radius are stable after reduction and can be immobilized in slight cockup or neutral position with radial deviation. They should, however, be followed very carefully to prevent or treat a change in position. When a cockup plaster gauntlet was used from the start in 5 favorable cases, healing took place within five to eight weeks. The method of Soto-Hall[10, 11] was used for fixation, except that the distal joint of the thumb was left free.

Most displaced Colles fractures cannot be held in dorsiflexion, however, and we have immobilized these in volar and ulnar flexion, changing the position to 20 to 30° of cockup in three or four weeks. This is very similar to the treatment of the scaphoid fracture associated with luxation of the lunate, since the lunate may also dislocate in a position of dorsiflexion.[11] Speed[13] and Cravener and McElroy[14] treated scaphoid fractures successfully in volar and radial flexion, although they do not recommend it now. We have treated the radius first because it heals first, with the important addition that the proximal phalanx of the thumb was included in the cast to prevent motion of the scaphoid fragments. This is easily done with a small amount of plaster, and prevents local resorption and cystic changes, which otherwise occur in a cast for the Colles fractures if the scaphoid fracture is not suspected. Six cases so treated have required nine to twenty weeks of immobilization for union to occur, and have needed extensive physiotherapy thereafter.

In 2 elderly patients of the series, in whom marked osteoporosis and vascular changes developed, active motion and physiotherapy were considered to be more important to the functional result than immobilization until bony union eventuated. Accordingly, after five or six weeks, casts were omitted and physiotherapy begun. We lost track of 2 other cases. Unfortunately, the follow-up study on all cases is not complete enough to warrant final conclusions of the best method of treatment.

Summary and Conclusions

Three hundred consecutive, recent fractures of the distal radius were complicated by fracture of the carpal scaphoid in 15 cases (5 per cent). The combination cannot be considered a rarity.

Diagnosis of the scaphoid fracture is difficult in presence of a radial fracture that dominates the x-ray picture and masks symptoms due to the fractured scaphoid.

Treatment of the combination presents a difficult paradox concerning position of immobilization. When possible, we have treated such injuries as though they were uncomplicated scaphoid fractures; when that could not be done, we have used volar and ulnar flexion of the wrist with inclusion of the proximal phalanx of the thumb in the cast to prevent motion of the scaphoid fragments. The position was changed to cockup in four weeks when there was no danger of displacing the radial fragments.

Figure 1. *Fractures of the Base of the Third Metacarpal and the Waist of the Scaphoid, with a Comminuted Colles Fracture of the Joint.*

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MEDICAL PROGRESS

ACTIVE IMMUNIZATION (Continued)

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PERTUSSIS

Results Obtained with Vaccine

Opinion regarding the efficacy of pertussis vaccine is still far from unanimous. Bell,[6] in a recent review of the subject, stated that "health officers have sufficient evidence to permit the use of [pertussis vaccine]." Lewis[174] sums up the conservative view, more widely held in England, that there is still a need for large-scale field trials, and that until these have been carried out no widespread campaign for whooping-cough inoculation in that country is justified. Parish[175] similarly expresses the belief that the laboratory and clinical evidence to date do not prove the effectiveness of specific immunization against whooping cough. Both workers have doubtless been considerably impressed by the flatly negative results obtained in the first extensive controlled study of the vaccine in England, reported three years ago.[176] This point of view was strongly expressed in a critical editorial, concurrent with the English report, which pointed out defects in many of the best known American studies of the vaccine — differences in family size or in time of observation of vaccinated and control groups, lack of any genuine controls and so forth.[177] It is true that some reports of apparently favorable results from pertussis vaccination do not stand up well to critical examination. As an example, one may cite the 436 immunized Winnipeg children observed by Brereton[178] in whom no whooping cough occurred in two and a half years, despite the occurrence of 1171 cases in the city during this period. Such findings suggest — but in no sense prove — that the vaccine used was effective. One may calculate that there should have been about 17 cases among his patients in this period if the vaccine had been ineffective — and if his patients were a representative sample of the child population. No evidence is presented, however, that his patients were not unduly shielded from infection (for example, that they had few or no siblings and limited contacts with other children) or were otherwise not representative of the community as a whole. More convincing, although likewise lacking in controls, is the experience of Tucker,[179] who has seen only 70 cases of pertussis among 5590 children immunized during the last thirteen years. A situation more subject to statistical evaluation is reported by Rodman, Bradford and Berry,[180] who observed a public-school outbreak, in which the incidence of pertussis was twice as high in the unvaccinated as in those who had received any pertussis vaccine, and almost six times as high as it was in those whose immunization had included at least 50,000,000,000 organisms. However, since the entire outbreak included only 57 cases, the results must be accepted with some reservations. During another outbreak, reported by Lapointe,[181] in a foundling home in Quebec, 82 per cent of 550 unimmunized children and infants contracted pertussis, with 5 deaths, whereas no more than 10 per cent of the 100 vaccinated children developed the disease. Despite the lack of a clear-cut basis for comparison between the controls and the children vaccinated, this report is hard to explain except on the assumption that vaccination was highly effective.

Bell[182] has recently reported a study that approaches the epidemiologist's ideal for evaluation of an immunization procedure. A diphtheria-immunization campaign for infants aged two to twenty-three months was conducted through a group of clinics in Norfolk, Virginia, with the co-operation of the local health authorities. Doctors and nurses were furnished alum-precipitated toxoids for the program, with instructions to administer certain lots if the baby was born in an "odd" month (such as January, March or May) and other specified lots if the birth had been in an "even" month. Neither the parents nor the local health authorities were informed that one set of lots also contained pertussis vaccine. The physician in charge of the study, who saw most of the cases of whooping cough reported by visiting nurses in the immunized children, did not himself know which lots had contained pertussis vaccine. In this fashion it was possible to ensure absolute impartiality on the part of the examining physicians and others engaged in collecting field observations. Statistical analysis showed that both groups were essentially identical in sex, age distribution, color, order in family, age at first inoculation, incidence of other common contagious diseases, and numerous other factors that might have biased the results of the study. These results showed an over-all incidence of pertussis in the controls, which was 3.45 times that in the patients receiving pertussis vaccine. If only frank severe pertussis was counted, the incidence was 8 times as great in the controls as in the vaccinated. In view of the fact that the total dose of alum-pre-

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cipitated pertussis organisms used was only 20,000,000,000, these results are impressive even by the most conservative standard.

Immunization of Young Infants

It has long been recognized that young infants have little or no inherited immunity to pertussis, and that most deaths and complications occur in this age group: "Over 50 per cent of all (pertussis) deaths occurred under six months of age and over 75 per cent died before reaching the age of one year."[183] It was formerly believed that infants under six months did not respond effectively to pertussis immunization; this may well have been true of earlier and less effective vaccines. At all events, numerous recent reports have testified to the contrary. Sako,[184] following up his earlier studies in this field, reports agglutinin responses in 8690 Negro children immunized at ages ranging from two weeks to five years. No significant differences in antibody response of children immunized at different ages were found. Four hundred and ninety-three children immunized before three months of age were known to have been exposed to pertussis within the household, and were compared to 438 exposed controls of comparable age. Pertussis occurred in 13.2 per cent of the vaccinated children and 89.7 per cent of the controls. Incidentally, the pertussis attack rate in the former was in general inversely correlated with their agglutinin titers — apparently the first strong evidence that agglutinin titers and protection against clinical pertussis are correlated. Sauer,[185] Adams,[186] di Sant' Agnese[94, 187, 188] and Halpern[189] among others, have also reported successful immunization of young infants, as judged by antibody titers or skin tests. Both Sauer and Sako emphasize the superior agglutinin titers produced by alum-precipitated vaccine as compared to fluid vaccine.

Most investigators have agreed with Sauer[190] in finding a poorer antibody response in early infancy than in late infancy and childhood, only Sako[184] reporting no evidence of such differences. To guard against early relapse of immunity in young infants given pertussis vaccine, many workers have stressed the importance of giving a booster dose of pertussis vaccine a year or so later. Confirmation of the efficacy of such a booster dose is presented by Sako,[184] by di Sant' Agnese,[94, 188] and by Kendrick and her associates,[191] who found ample antibody responses to such injections, the response in di Sant' Agnese's series, however, being definitely better in infants first immunized at six to twelve months.

Preparation and Testing of Vaccine

Obviously, even the best results reported with pertussis vaccine are not wholly satisfactory. The principal difficulty at present lies in insufficient knowledge regarding the antigenic factors responsible for producing immunity to the disease. Recent advances in the purification of the endotoxin[192] and the soluble antigens[193] of the pertussis bacillus may furnish a basis for more exact knowledge in this respect. Meanwhile, experiments with cruder preparations, or whole organisms, have contributed much fundamental knowledge. Proom[194] has shown that studies of experimental infection may give different answers depending on the technic employed — for example, intraperitoneal injection of live pertussis organisms in a mouse produces chiefly a toxemia, combated successfully by antitoxin, whereas intranasal infection is best counteracted by antibacterial antibody. Evans,[195] long experienced in the study of pertussis toxin, has recently added to the accumulation of evidence that antitoxic antibodies are apparently not of material significance in human infection or immunity, and Verwey and Thiele[196] have added to the parallel evidence in animals. Gray,[197] in animal experiments, has reaffirmed the importance of young, virulent cultures in the preparation of potent immunizing agents, and his more recent observations suggest that much is yet to be learned regarding the ideal conditions for production of vaccine.[198] A new and somewhat obscure factor has been added with the finding that both virulence and antigenicity of pertussis bacilli are closely related to a hitherto unrecognized property — the ability of pertussis cultures to agglutinate avian or mammalian red cells.[199] If this can be adequately confirmed, it may provide an extremely useful tool for further evaluation of stock cultures for vaccine production, for screening of vaccine batches for potency and perhaps for confirmation of the clinical diagnosis of pertussis. The procedure is as simple as the Hirst test, to which it is analogous from a technical viewpoint.

Potency evaluation of pertussis vaccines by a laboratory technic has long been beset by difficulties in reproducing a clear-cut disease in animals, as a challenge of experimental immunization. Kendrick and her associates[200] have carried out an extensive study, in collaboration with numerous other laboratories, using the intracerebral route for injection of the challenge organisms in mice; their results indicate marked differences between different batches of vaccine. However, the highly artificial character of the intracerebral route in contrast to the nasal route, for example, leaves room for dispute concerning which is the most useful in performing a potency test. The nasal route has long been known and is widely employed[194, 197]; to date it has shown the disadvantage of giving highly variable results. When the inherent difficulties in evaluating the potency of pertussis vaccine can be resolved, and laboratory and field trials have been extensively correlated, it will be possible to make more rapid advances in preparation of the vaccine or of its active fractions.

Meanwhile, the possibility has arisen that pertussis vaccines — like typhoid vaccines — will have to be prepared in polyvalent form. Wilson and Miles[201] have noted that it may ultimately prove necessary to include the parapertussis organism in pertussis vaccines. With such a thought in mind, Rambar, Howell and Denenholz[202] have prepared a combined pertussis-parapertussis vaccine that produced clear-cut opsonic antibody rises against both components and actually appeared to induce a better response against the pertussis bacillus than that obtained with the monovalent pertussis vaccine.

Reactions

Since the start of extensive whooping-cough immunization, reactions to the injection of the vaccines used have been sufficiently frequent to cause occasional concern. Local tenderness and swelling have been ascribed to the use of too concentrated a suspension, or to the irritating effects of alum precipitates. Lapin[203] found that variations in concentration of organisms from 15,000,000,000 to 40,000,000,000 per cubic centimeter caused no significant difference in incidence of local or general reactions. He believes that the irritating effects of alum are due chiefly to its low pH. Sterile abscesses (or "antigenic cysts"), which may occur in as many as 2 or 3 per cent of cases, are usually associated with alum-precipitated preparations. Tucker[179] and Sauer[185] stress the importance of injecting distally, and carefully wiping free alum off the needle tip before injection, to avoid alum abscesses. Sako[184] employed these precautions as well as the recommendation of Bell[182] that deep subcutaneous injection be employed, and he added the precaution of taking especial care to avoid intracutaneous injection. Following these precautions, he observed 1.5 per cent "alum abscesses" in 2021 inoculations. On the other hand, other reactions were more than twice as frequent with fluid vaccine as with alum-precipitated material.

A matter of more serious concern is the occasional occurrence of convulsions or, more rarely, of a frank encephalopathic syndrome following pertussis vaccination. Sako[204] noted 2 cases of vomiting, diarrhea and convulsions in his earlier series, and several similar reports have been cited by Byers and Moll,[205] including 4 fatal cases. Brody and Sorley[206] reported the case of a ten-month-old infant who exhibited generalized hypotonia, somnolence and difficulty in micturition following each of three doses of pertussis vaccine. At the age of forty-three months he received a skin test with pertussis vaccine, after which a generalized flaccid paralysis developed, the patient dying of bronchopneumonia seven weeks later. Byers and Moll[205] have collected 15 cases of convulsions following pertussis-vaccine inoculation, which were seen at the Boston Children's Hospital over a ten-year period. Thirteen exhibited residual damage when last seen. It is difficult to evaluate such findings, since many other causes of encephalopathy exist, and the association with pertussis vaccination might conceivably be one of coincidence. The absence of comparable reports from other communities may be reassuring, but this cannot be evaluated until others have searched for this syndrome as extensively as Byers has done. Approximately 40 cases of possibly similar nature have been disclosed through individual case reports[207] and an extensive questionnaire sent to some 55 physicians whose collective experience covers at least several hundred thousand injections.[208] The net impression gained from this survey is that such reactions may occur, but that they are exceedingly rare. Meanwhile, the National Institute of Health has during the two years developed a toxicity test for pertussis vaccines. The application of this test may serve to eliminate excessively toxic batches of vaccine, which may have been responsible for reactions of the type described.

Pneumococcal Pneumonia

Immunization with Bacterial Suspensions

The capacity of extracts from cultures of pneumococcus to furnish protection against pneumococcal infection in animals was demonstrated over fifty years ago.[209] An understanding of the immunologic and chemical properties of the specific soluble substance of the pneumococcus did not come about until much later, however; hence early attempts to immunize human beings against lobar pneumonia were carried out with the use of whole bacterial vaccines. The most widely cited of these studies[210, 211] yielded promising results. Cecil and Austin,[210] for example, in a study at Camp Upton, inoculated 12,519 "stable" troops with a vaccine composed of Types 1, 2 and 3 organisms, using about 20,000 other troops (of which perhaps 75 per cent were "stable") as controls. The incidence of Types 1, 2 and 3 pneumonia, over a period of ten weeks, was nil in the vaccinated and 18 in the comparable stable control group. However, since the incidence of other types of pneumonia — particularly those due to the streptococcus — was likewise greater in the controls than in the vaccinated, the validity of this experiment is open to question. The South African studies of Lister and his colleagues[211-214] cover longer periods and larger groups, among native laborers in the goldfields. However, no actual controls to these groups were set up, so that the results from vaccination had to be evaluated by comparison with the incidence of pneumonia in unvaccinated mine groups, or in years prior to vaccination. Although the results strongly suggested that vaccination was materially effective in some cases at least, there are alternative explanations for the figures observed, and there are some figures showing less promising results.[215] Hence this series of studies must also tentatively be regarded as inconclusive.

Immunization with Specific Polysaccharides

As the number of recognized types of pneumococcus increased, and it became established that each was immunologically distinct, the possibility of effective human immunization against pneumococcal pneumonia was generally laid aside, and efforts were directed toward its treatment by physiologic and serologic means. However, the chemical studies of Dochez, Avery and Heidelberger[216, 217] made available in purified form the specific soluble capsular polysaccharides that characterized several of the common types of pneumococcus. Francis and Tillett[218] showed that intracutaneous injection of these preparations into patients with pneumonia gave rise to antibody formation; this was confirmed, in normal as well as sick persons, by Finland and Sutliff.[219] Earlier disagreement regarding the antigenicity of such preparations in mice — the customary test animal[220] — was shown to be due to the existence of two forms of the antigen: the natural acetylated form, and a deacetylated form resulting from treatment with alkali.[221] Both were found to be antigenic in man, but only the former induced antibodies in mice.[222]

Felton[223, 224] carried out extensive laboratory-controlled studies on the use of specific polysaccharides of pneumococcus in man. He demonstrated that significant antibody responses could be induced by doses of polysaccharide that were reasonably well tolerated by the recipients. His work formed the basis for collaboration with Army Medical Corps personnel, in a study of immunization against Types 1 and 2 pneumonia in about 70,000 males, mostly under twenty years of age, in New England and the far West.[225] The incidence ratio of Types 1 and 2 pneumonia in 14,000 controls as against 10,700 persons vaccinated in New England was about 1.7:1; but in the much larger western groups (26,000 control and 18,000 vaccinated subjects) the relative incidence was 9:1. However, because of the short season of observation, the lack of strict alternation in selecting the controls, and other factors, these impressive results must be taken with some reservations.

Similar studies on a smaller scale, carried out in several localities over the past decade, have given varying results, which either were not numerically significant or might readily have resulted from natural fluctuations in the incidence of pneumonia. However, there have recently been reported two series of studies in which the results obtained appear to be significant. MacLeod and his associates[226] immunized 8586 soldiers at a technical school, with 0.03 to 0.06 mg. each of Types 1, 2, 5 and 7 polysaccharides, 8449 controls being injected with phenolized saline solution. Age distribution, duration of service and so forth were closely comparable in both groups. The high incidence of pneumonia at this school in two preceding years favored such an immunization study. Laboratory studies, both on the Army group and on civilian volunteers, had shown, moreover, that such inoculation was followed in almost all cases by striking increases in the specific precipitating antibody titer in the subjects' serum.[227, 228] The incidence of the four types in question, during an average stay of twenty-four weeks per man, was 4 cases in the vaccinated, and 56 in the controls. Furthermore, the carrier rate dropped significantly in the vaccinated group, this drop no doubt contributing to the apparent decrease in the number of cases of Types 1, 2, 5 and 7 in the *controls*, which was only 17 per cent of the expected rate based on the incidence of higher types not affected by the study. Taking the bacteriologic and epidemiologic data as a whole, the effect of polysaccharide immunization in this group appears to have been striking.

Kaufman[229] has recently reported a six-year study of immunization in elderly persons with Types 1, 2 and 3 polysaccharides. A group of 5750 immunized subjects contracted 3 cases of Type 1, 2 or 3 pneumonia (and 31 cases of other types of pneumococcal pneumonia) during this period, whereas 5153 controls experienced 96 cases of pneumococcal pneumonia, of which 33 were Types 1, 2 and 3.

Serum titrations before and twenty-one days after immunization showed increases of several hundred times in antibody content after injection of the antigens. Local reactions occurred in 5 per cent, and general reactions in 2 per cent of the subjects. In patients who developed pneumonia, the duration of illness and the severity of toxemia were less in the immunized than in the controls. Total person-years of observation are not given, nor is the method of selection of controls stated; the peculiarly higher incidence of "higher types" of pneumonia among the controls is not explained.

Nevertheless, the sum total of all available observations cited above strongly indicates that immunization with pneumococcal type-specific polysaccharides exerts a strong protective effect in man against the homologous types of pneumonia. Such polysaccharide preparations have recently been put on the market, in two forms: a mixture of Types 1, 2, 3, 5, 7 and 8, primarily for use in adults and adolescent children, and a mixture of Types 1, 4, 6, 14, 18 and 19, for protection of infants and young children against the types to which this age group is most subject. Both these multiple-antigen preparations have been shown to be effective in stimulating antibody production.[230] The Massachusetts Department of Public Health has recently called attention to the value of such immunization, recommending that it be considered in the elderly, the very young, special occupational groups with high natural incidence of pneumococcal pneumonia and patients about to undergo major surgical operations.[231] If immunization is employed for this latter category, however, it should be borne in mind

that such immunity as may develop cannot be expected to appear for at least nine days, and will probably not be adequate in less than two weeks after inoculation. Also, it is imperative to re-emphasize the fact that immunity induced by pneumococcal polysaccharides is effective only against the homologous types of pneumococcus, except where a low degree of cross immunity against related types may be induced.

Rabies

Present Situation; Dog Vaccination

Although rabies has been on the wane in certain areas, notably New England, it has been definitely on the increase elsewhere in the United States during the last few years. This trend is clearly set forth in a recent review by Johnson,[232] who summarizes the epidemiology, etiology, laboratory characteristics, symptoms in animals, diagnostic features and preventive measures applicable to the disease, in a presentation distinguished for its clarity and readability. The review calls attention to the marked increase in animal rabies in recent years over the United States as a whole; the number of reported rabid animals throughout the country was higher in 1944 than in any previous year on record. In fact, the spread of this disease among animals in New York, Pennsylvania, Maryland, Virginia and other states in the last few years has led to several studies and conferences from which have come broadly conceived, long-range programs for control of the disease on a nationwide basis.[233, 234] Such control is needed not only because of the risk to human life engendered by the disease, and the discomfort, inconvenience, expense and actual danger incurred by persons receiving the vaccine, but also because of the considerable loss in farm stock caused by rabies: there were 2800 reported deaths from this disease among cattle alone during the period 1938-1945 inclusive, the actual number being unquestionably much higher.

Johnson's review, the New York Academy of Medicine Report, and the April 1947 conference headed by Dr. R. A. Kelser, all agree on the following recommendations:

> Rabies control can only be accomplished effectively through federal participation and co-ordination — the agencies most obviously concerned being the United States Public Health Service, the Bureau of Animal Industry and the United States Fish and Wildlife Service.
>
> Reporting of animal rabies should be universally required.
>
> Dog licensing should be enforced, stray dogs should be impounded, and dog quarantine should be applied, especially in areas where animal rabies is present.
>
> Dog vaccination should be encouraged on the widest possible scale, and at little or no cost to the dog owner (since few owners will avail themselves of the service otherwise). In urban areas, dog licenses should be made contingent upon vaccination.

A widespread and generalized public-education program should be undertaken, particularly to acquaint the public with the need for control of rabies, the advantages of rabies control to dogs as well as man, and the now proved value of dog vaccination. Johnson[232] remarks upon the still persistent belief that dog vaccination is ineffective—a belief based upon the poorly conceived experiments and low-potency vaccine of some years ago. The effectiveness of a potent vaccine, properly used, is shown in an experiment of his, referred to elsewhere[233]; 52 vaccinated dogs, along with 52 unvaccinated dogs, were injected with street virus one year after vaccination. Death occurred in 11.5 per cent of the vaccinated as against 79 per cent of the control animals. Such experiments as these and other experimental and field studies previously cited[11] have established the efficacy of dog vaccination. Its practical value has also been recently affirmed in New York State; in ten counties having 78 per cent of the enumerated dogs vaccinated, the incidence of rabies in unvaccinated dogs was fifteen and eight-tenths times that in the vaccinated animals.[235] The value of protection of one's pets is also illustrated in the saga of a rabid dog that recently roamed through three townships before it was killed, and bit 13 unvaccinated dogs in succession—several of which had to be destroyed as a result.[236] Effective control of rabies, however, cannot be achieved merely through local or even statewide programs, since rabid animals do not recognize state boundaries. Hence the recommendation[232, 234] for federal rabies-control legislation is especially pertinent at this time of increasing prevalence of the disease in animals.

Methods of Preparing Rabies Vaccine

The factors that may influence the potency of rabies vaccine continue to be under scrutiny. Habel[237] compared the potency of vaccines inactivated by ultraviolet irradiation, by phenol and by chloroform, and found the ultraviolet-treated material to be greatly superior. A new method of inactivation, employing nitrogen mustards, has been applied experimentally,[238] but has not yet had extensive trial in either animals or man.

The choice of virus strain for preparation of vaccine may still be open to question, since Habel and Wright[239] found marked differences in immunizing potency of six different strains in routine use. Their paper gives a detailed description of what is now the standard method for testing the potency of rabies vaccine. The standard of potency set under this method is considerably higher than the average level that prevailed before the method was pro-

mulgated, so that the vaccines now obtainable may be used with far greater assurance of efficacy than before.

Although greatly improved in potency, the currently available vaccines contain large amounts of impurities in the form of brain-tissue constituents. Because of the numerous recent studies noted below, which indicate that brain-tissue injections may induce severe damage to the nervous system, present interest is focused on the problem of purifying the vaccine. Two recent reports[240, 241] have described methods for removing most or all of the lipid constituents of the vaccine, by extraction with organic solvents at low temperatures. The resulting preparation appears to be actually more potent than the crude material.[240]

Reactions Following Antirabic Vaccination

Paralytic accidents following administration of rabies vaccine have been found to occur about once in 5800 cases, with death resulting in about 1 out of each 23,000 cases treated.[242] The incidence fluctuates greatly, however; after more than a decade during which no fatal cases were noted in Massachusetts, 2 deaths occurred in 1947.[243] A high incidence of such accidents has also been recently noted elsewhere.[244, 245] Irrespective of whether such accidents are sporadic or represent a definite upward trend, the 2 recent deaths in this state have served as a reminder that the use of rabies vaccine must be considered in the light of the total situation. In Massachusetts, for example, endemic animal rabies has not been present for four or five years. Here rabies vaccine can wisely be withheld except in cases of proved exposure to the disease, or in persons bitten in the Berkshire area, which is subject to reinfection at any time by rabid animals from the neighboring endemic foci in New York State. The advisability of such a conservative review of the problem has been stressed by the Massachusetts Department of Public Health[243] and in an accompanying editorial in the *Journal*.[246] Sellers,[247] whose experience has been gained in one of the most heavily rabies-infected areas in this country, shares the view that antirabic vaccination is not to be lightly undertaken, stating his belief that "it has caused more deaths than has rabies when given to persons only indirectly or remotely exposed." He notes that in the 7 cases of treatment paralyses that he has followed, 4 patients died; only 2 of these 7 were in persons bitten by rabid dogs, the other 5 (including 3 of the deaths) occurring in persons only remotely exposed to rabies.

For a number of years it has been suspected that encephalitis following rabies vaccination might be the consequence of an iso-allergic reaction resulting from injection of brain substance, which is organ-specific rather than species-specific. Some years ago Rivers and his associates[248, 249] succeeded in producing lesions in the nervous system of monkeys by repeated injections of suspensions and alcoholic extracts of rabbit brain. Recently, Morgan[250] and Kabat, Wolf and Bezer[251] have produced encephalomyelitis in monkeys by a few injections of brain substance combined with tubercle bacilli, paraffin oil and an emulsifying agent, according to the technic developed by Freund.[143] Using guinea pigs, Freund et al.[252] produced meningoencephalitis and paralysis of the hind legs with only one injection of such an emulsion of brain tissue. Furthermore, some of the animals surviving the first injection developed acutely fatal reactions after reinjection of the same material three or four weeks later. Kopeloff and Kopeloff[253] confirmed these findings in guinea pigs, and produced paralysis by similar means in rabbits. Recently, Jungeblut[254] has added further confirmatory evidence of the sensitizing capacity of brain substance. Thus, there are ample experimental data to indicate that repeated injections of brain substance can, under certain as yet obscure conditions, induce an iso-allergic reaction that may result in varying degrees of destruction of the gray and white matter of the brain or spinal cord. It is, of course, yet to be proved that human paralytic accidents are caused by such a reaction, but the available evidence points in this direction. Still to be explained, however, is the relative rarity of such reactions.

The experiments cited provide a basis for attempting to define the specific substance or substances in brain tissue that are responsible for these reactions, and to develop physical or chemical methods for their removal. Recent purification studies[240, 241] may lead to such findings, but this has as yet to be determined. A different approach to the solution of this problem is suggested by Chen-Jen and Zia,[255] who have prepared a potent vaccine from rabies-infected brains of guinea-pig fetuses, fetal brain tissue having been found by Zia[256] and others[251] to be apparently nonantigenic. Meanwhile, this and other aspects of the problem are now under active investigation in several laboratories, and it is to be hoped that these studies will be fruitful.

Smallpox

Recent Occurrence of Virulent Smallpox in the United States

On the whole, the incidence of smallpox has continued to decline in the continental United States during the last few years. This decline has recently been the subject of an editorial comment,[257] which cited Dr. Benjamin White's[258] reminder of over twenty years ago, that smallpox is never conquered, but "is at best only held at bay by the continued practice of vaccination." Recent experience in the Orient, on the West Coast of this country and later in New York City has amply confirmed this already well established fact. The severity of smallpox as seen in the Orient, as well as the frequency

of its occurrence in presumably vaccinated persons, was vividly described a year ago by Agerty,[259] who observed 17 cases with 10 deaths among American personnel in Japan. Only 4 of these patients had histories or scars indicating that they had been vaccinated in childhood. All but 3 had been recorded as having been vaccinated within the preceding two years; in 2 vaccinoid reactions had developed, the other 12 being noted as "immune," "doubtful" or "unsuccessful." (The probable significance of "immune" reactions is discussed below.) Reports from other sources have indicated scattered failures to protect American personnel in the Orient by the use of the standard vaccination procedure and the vaccine available at the time. Hence it was not surprising that cases appeared among servicemen returning to the West Coast. Such cases caused a small outbreak in San Francisco early in 1946,[260] and a much larger one in and around Seattle.[261, 262] The latter outbreak produced at least 65 cases with 20 deaths (a 30.8 per cent case mortality) and took four months to stamp out. An incidental result of this outbreak was an unprecedentedly successful vaccination campaign in neighboring British Columbia, which probably reached 250,000 people. This may be contrasted with the 80,000 in the province who submitted to vaccination fourteen years earlier in the presence of an actual smallpox outbreak. Apparently, the public at large has become widely educated, in the interval, regarding the wisdom of being vaccinated.[263]

If proof of this acceptance of vaccination were needed, the New York City outbreak of March–April 1947 has furnished it. A total of 8 confirmed cases in New York City, and 4 outside the city, occurred over a period of about six weeks. The findings in most of these cases have been thoroughly expounded and discussed in a clinicopathological conference.[264] The first case was atypical and not recognized until secondary cases were diagnosed, by which time it was evident that numerous scattered tertiary cases might be expected to appear. The decision was therefore made to vaccinate the entire city. Over 6,000,000 people were actually vaccinated during the following two weeks.[265] This was accomplished by extraordinary efforts on the part of local medical and health personnel and also of the producing firms, which were faced with a demand for vaccine unparalleled both in size and in urgency. This outbreak caused widespread alarm elsewhere, increases in vaccination demands being observed at least as far away as Michigan. Although states such as Massachusetts and Michigan, having their own production facilities, were able — with difficulty — to keep pace with the demand, many other communities saw their supplies of vaccine temporarily exhausted. The experiences of the last two years suggest that it is entirely possible for several virulent foci of smallpox to be established in this country at about the same time. In such an event, vaccine supplies would certainly be temporarily inadequate. This possibility focuses attention on the importance of maintaining an immune population, by vaccination in infancy and periodic revaccination.[266] This is clearly demonstrated by the New York experience, which showed that perhaps 50 per cent of the people in that urban area were susceptible to infection, as indicated by either a primary or a vaccinoid reaction.[5]

England has had similar but considerably more numerous experiences, as indicated in several excellent reports of outbreaks of virulent smallpox in that country.[267-272] Mortality rates have been high — for example, 3 deaths in 11 cases,[268] 9 in 31 cases,[269] and 6 in 30 cases.[271] Control has been difficult owing to unfamiliarity of local physicians with the diagnosis; to the high level of susceptibility in England, where compulsory vaccination has always been resisted and in fact has recently been abandoned[273]; and to the marked and prolonged contagiousness of infected materials, smallpox crusts sometimes remaining infectious for as long as a year.[274]

Interpretation of Vaccination Reactions

The extensive need for mass vaccination during and after World War II and the many opportunities for contracting smallpox confronting persons hitherto safe from the disease have led to an extensive and critical re-evaluation of the phenomena of vaccination. The official requirement of a vaccination certificate, imposed on an unprecedented number of travelers, gave rise to various problems, outstanding among which was the question of how to interpret an "unsuccessful vaccination," especially in persons who failed to develop a "take" after repeated attempts. For example, Broom[275] reports the experience resulting from vaccinating 1227 UNRRA personnel, 238 of whom did not "take." On revaccination of 201 of this group, 80 per cent were again negative. Broom suggests that such persons are "insusceptible" to vaccination, and that allowance should be made for such a classification on vaccination certificates. He is supported in this by Mitman,[276] MacKenzie,[277] Stuart[278] and, indirectly, also by Cavaillon,[279] who suggests that it may be desirable to indicate, "in unsuccessful cases, that vaccination had been carried out twice or several times, at certain intervals." In fact, some observers have regarded "no reaction" as synonymous with immunity,[280] but such views run into direct conflict with the prevailing belief, at least in this country,[281] which holds that unsuccessful vaccination is never to be accepted as final and merely calls for another attempt. However, it must be recognized that such a doctrine can be incompatible with the realities of human activity, as the medical officer of the Port of London has cogently pointed out[282]; for example, a traveler cannot ordinarily

postpone a sailing date until a long series of attempts at revaccination is at last successful.

A significant portion of the difficulty in obtaining satisfactory "takes" appears to derive from ineffective technic of vaccination. Several recent English communications have called attention to the deficiencies of the scratch technic which has been generally used in that country. Mole,[283] performing alternate scratch and multiple-pressure vaccinations, obtained 83 per cent "takes" by the scratch method as against 94 per cent by the multiple-pressure technic. Vaughan[284] and Lovett[285] similarly report repeated successes in multiple-pressure vaccination, in persons previously scratched unsuccessfully by the older technic. Within the past year the use of the multiple-pressure method (which Parish[286] and others in England have advocated for several years) has been officially recommended by the British Ministry of Health[287] and by an expert committee of WHO on International Epidemic Control.[288] It will be of interest to observe whether the problem of "insusceptibility" is diminished in the future as a result of this trend. In justice to the scratch technic, however, it should be noted that on occasion almost complete success has been achieved by its use. When smallpox appeared on a troopship bound for New Zealand, 94 per cent of the 1648 men on board were successfully vaccinated by the scratch method on the first attempt.[289]

A subtler problem arises from the interpretation of the so-called "immune reaction" —the raised papule that reaches its height on the second or third day and then subsides without vesicle formation. This reaction is very widely accepted as adequate evidence of immunity. Doraisingham,[290] for example, notes that smallpox in Singapore has been extremely rare for thirty years, in a population of which 73 per cent (in a large sample) gave an "immune" reaction to vaccination; he regards this as strong evidence that such a reaction represents genuine immunity. But it has been known for many years that heated, inactivated vaccine virus can produce a papular reaction indistinguishable from that caused by live virus. This was well shown by Andervont and Rosenau,[291] and by MacKinnon and Defries[292] among many others, and has been recently confirmed.[275, 293, 294] Benenson[294] has carried this farther, showing that heated and unheated vaccine from the same batch can even produce identical *vesicular* reactions. Thus, it is not always possible to tell whether the result observed was caused by live or dead virus. Furthermore, he has shown that the production of a papular or vesicular lesion with heated virus is not ordinarily associated with a serologically demonstrable immune response. Using the complement-fixation test and the agglutinin-inhibition technic developed by Nagler,[295] Benenson and Kempe[296] have demonstrated that an early immune type of reaction produced by live virus is generally accompanied by a rise in the subject's serum antibody titer, but that no such rise is observed if heated virus is used. Benenson therefore believes — agreeing in this instance with Mitman[276] — that a reaction to vaccination that reaches its height within seventy-two hours is quite literally uninterpretable. If this proves to be the case, an early reaction can no longer be regarded as evidence of successful revaccination, and the vaccinator must depend for success, in such cases, entirely upon proper technic and the assurance of a supply of fresh, potent vaccine. Thus it again becomes evident that successful revaccination depends very largely upon observance of the expiration date on each package of vaccine, and also upon the utmost diligence in keeping the vaccine frozen when it is not actually in use or transit.

Little help has been offered by way of varying the route of administration of smallpox vaccine; a recent report from Finland indicates that long-term immunity in 369 cases following subcutaneous vaccination was lower than that produced by scarification.[297]

Technic of Preparing Vaccine

It is still commonly stated[298] that sterile — that is, bacteria-free — smallpox vaccine cannot be produced in calves. Numerous workers have reported the use of penicillin to reduce the bacterial count in such vaccine. Equally striking results can be obtained, however, by the use of a quaternary ammonium detergent, such as "roccal," during incubation of the virus and while the vaccine is being harvested from the animal used.[299] The effectiveness of this method has been amply confirmed by Dr. J. A. McComb at the Massachusetts Antitoxin and Vaccine Laboratory, where bacteria-free preparations of ample potency have been repeatedly obtained. Many other institutions have assuredly done likewise.

Smallpox vaccine produced in fertile hen's eggs has not received wide acceptance as yet, but it has been in general distribution in Texas for several years. Of 779,250 doses distributed in that state, reports were obtained on 125,892 vaccinations, 87.3 per cent of which gave primary, accelerated or "immune" reactions. In a group of 39 persons vaccinated with chick-embryo vaccine one to five years previously, revaccination with calf vaccine gave 35 immune and 4 accelerated reactions. Thus, the duration of immunity produced by egg vaccine appears to be within normal limits. The egg vaccine was reported to have caused milder local reactions, smaller vesicles, less secondary infection and less systemic disturbance than the standard calf vaccine.[300] However, until egg vaccine has been shown to be effective in stopping a smallpox epidemic, it will apparently not be generally accepted by health authorities, since the merits of calf vaccine in this respect are already well established.

Complications

Eczema vaccinatum continues to occur occasionally here[301] and elsewhere in eczematous children who are permitted, through ignorance or error, to come in contact with recently vaccinated persons. Such patients still occasionally die,[298] very much more rarely than before chemotherapeutic agents were available and modern knowledge of the care of such patients was developed. Two deaths were observed among 36 cases arising in conjunction with the mass vaccination of 6,000,000 people in New York City last year.[5] Excellent descriptions of 16 of these cases, with a review of the pertinent literature, have recently appeared.[302] Fifteen other cases in the same outbreak have been described separately.[303]

Post-vaccinal encephalitis remains, in this area, a very rare complication. Even cases reported as such are not always correctly diagnosed. Cavaillon et al.[304] report that, among over 1,000,000 vaccinations in the Paris area after a recent smallpox outbreak, notifications of 2 cases of "post-vaccinal encephalitis" were given; on post-mortem examination, however, death was found in both to have been due to bronchopneumonia. An analogous instance occurred in Boston a few years ago. In some countries, however, true post-vaccinal encephalitis occurs in sporadic outbursts of puzzling nature and localization. In and around Basel, 6 cases occurred among 30,000 vaccinations in the urban district in 1945, and 9 more occurred in the rural environs, whereas in Berne no cases occurred among 100,000 vaccinations.[305] In a very comprehensive summary of reports of this disease from all parts of the world, Stuart[306] notes case incidences ranging from 1 per 641 vaccinations (Tyrol, 1929) to none in over 1,000,000 (France, 1923-1928, and Italy, 1927). The evidence is clear that this complication is persistently recurrent in some areas, and virtually nonexistent in others, without relation to the source of the vaccine used, the manner of use or any other known technical factor. All reports agree that the incidence is far less in infants under three years of age than in older subjects[280, 306]; it appears also to be rarer after revaccination, although 26 cases following revaccination have been observed in Holland.[306] The limited experience in treating post-vaccinal encephalitis with convalescent serum — chiefly in England — is equivocal; 8 of 14 treated patients from 1940 to 1945, inclusive, recovered as against 21 recoveries in 44 untreated cases.[307] There is a fifty-fifty chance that this difference was accidental.

To the collection of miscellaneous and bizarre reactions to vaccination there has been added a report from England of a high incidence of evanescent photosensitization rashes resulting from the combined effects of sulfanilamide, sunshine and vaccination. Rashes did not appear in persons in whom vaccination had failed or been refused. The mechanism of the reaction remains unexplained.[308]

Many thoughtful investigators have considered the possibility that vaccination might cause abortion or fetal malformation in a pregnant woman. During the recent city-wide vaccination program in New York City, Bellows, Hyman and Merritt[309] observed the effect of vaccination on pregnancy in a series of 720 vaccinated women and 173 controls. No significant differences were demonstrated between the vaccinated and control groups in the incidence of malformation, stillbirth, abortion or infant deaths.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 35281

PRESENTATION OF CASE

A forty-seven-year-old housewife was admitted to the hospital complaining of abdominal swelling.

Thirteen years before admission, following the birth of normal twins, the patient developed a post-partum psychosis with hallucinations. She was in a mental hospital for about two years, but improvement was incomplete. At home, during the subsequent decade, she remained mentally disturbed, but tended the house. Her appetite was always very poor, and her diet was fair, with few eggs and rare fish and meat. Her menses were normal until fifteen months before admission, when amenorrhea and hot flashes appeared. Subsequently she felt increasing fatigue, anorexia and weight loss, with intermittent numbness and tingling in her feet. Her physician prescribed vitamins and administered liver injections, without improvement. The symptoms increased in severity during the year before admission. Her legs and hands had occasional episodes of tingling. In the month before admission she noted weakness of her legs on walking and climbed stairs with difficulty. In the few months just before admission she also noted that her legs had a tendency to develop ecchymosis easily on trauma, and she had occasional retching in the morning. For six months before admission, she consumed 5 or 6 ounces of whiskey and a bottle of beer daily in the hope that her appetite would be stimulated. There was no favorable response, however, and she ate about a fourth of a normal food portion. Ten days before admission, she developed watery diarrhea, which cleared up in two days. She felt weak, and one week before admission noted that her abdomen was swelling, and that there was mild ankle edema. She went to bed. Two days later her eyes were yellow, and her urine dark brown. No abnormality in the stools was noted. Abdominal swelling increased in the few days before admission.

She had never been jaundiced before, and had not been exposed to other jaundiced people. There was no history of gall-bladder disease.

Physical examination showed a thin, tremulous, icteric woman with a mousy odor to her breath. Her abdomen was tense and distended, and shifting flank dullness was present. There were no periumbilical dilated veins. The liver was enlarged to midway between the costal margin and umbilicus.

The edge was very firm. The spleen was not palpable.

The blood pressure was 90 systolic, 65 diastolic. The temperature was 99°F., the pulse 100, and the respirations 20.

Examination of the blood showed a white-cell count of 26,000, with 79 per cent neutrophils, 12 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The hemoglobin was 11 gm. The urine was dark amber, with a specific gravity of 1.013 and gave a ++++ test for bile. The stools were soft brown and guaiac negative. The alkaline phosphatase was 21 units, the nonprotein nitrogen 18 mg., the albumin 2.85 gm., and the globulin 2.69 gm. per 100 cc. The cholesterol was 180 mg. per 100 cc., and the sodium 125.2 milliequiv. and the chloride 78 milliequiv. per liter. The van den Bergh reaction was 5.6 mg. per 100 cc. direct and 7.2 mg. indirect, and the cephalin-flocculation test was ++ in forty-eight hours. The prothrombin time was 23 seconds (control, 15 seconds).

On x-ray examination the findings in the chest were not unusual, and the findings in the esophagus were suggestive but not diagnostic of varices.

On the second hospital day an abdominal paracentesis yielded 2100 cc. of slightly greenish fluid, with a specific gravity of 1.008 and 130 red cells and 20 lymphocytes per cubic millimeter. The patient did poorly. On the third hospital day alimentation with Levine-tube feedings was instituted. She became disoriented, and then unresponsive. The icterus did not increase, but ascites rapidly reaccumulated. The temperature rose to 102°F., and the white-cell count reached 40,000.

The patient's condition continued to deteriorate, and she died on the ninth hospital day.

Differential Diagnosis

Dr. C. W. Fairlie: When a woman enters the hospital with a history of ascites and jaundice for one week and dies within nine days, we have to assume that she died from liver disease. The questions are, What kind of liver disease and what precipitated this rapid demise? The first thought that comes to mind with so rapid a fatality is acute yellow atrophy or acute necrosis, but I do not believe that the patient had this condition. I think, rather, that she had a long-standing cirrhosis with some catastrophe superimposed that caused the final decline.

I will review the history in search of clues toward this conclusion. The mental illness I can make nothing of except that it contributed to her having apparently a subnormal diet over a period of ten or more years. The amenorrhea appeared just at the onset of her symptoms, fifteen months before admission. Since it was accompanied by hot flashes, I doubt that it was amenorrhea due to debilitating disease but rather was the menopause appearing at the age of forty-seven. The symptoms of anorexia, fatigue and weight loss for fifteen months are common in cirrhosis, but they are frequent in other conditions. The tingling and numbness in her legs suggest peripheral neuritis, but this was never confirmed by other evidence. The alcohol intake is not noted until the mention of its use as an appetizer for six months before entry, but one who turns to this amount of appetizer and continues it even though it is not helping has probably enjoyed the medicine before. Diarrhea was noted ten days before admission and did not recur. A mousy odor to the breath is mentioned. Interpretation of this finding is difficult from the printed word or, indeed, from examining the patient. The liver was enlarged to midway between the costal margin and the umbilicus, and the edge was firm. That is an important observation and would be most unlikely in a patient about to die, nine days later, from acute yellow atrophy of the liver.

The white-cell count of 26,000, and later of 40,000, must be a clue to the underlying process, but not a very specific one. It can occur in acute necrosis of the liver. However, it could also occur with infection or with severe hemorrhage. The phosphatase of 21 Bodansky units per 100 cc. is higher than that usually seen with parenchymal liver disease but such exceptions are becoming increasingly familiar. Regarding the albumin and the globulin, it is a pleasure to see them stated as such with no reference to the ratio obtained by dividing these two unrelated quantities one into the other. The low albumin is suggestive of long-standing liver disease but could occur with acute hepatitis or acute necrosis also. The sodium of 125 milliequiv. per liter, together with the blood pressure of 90 systolic, 50 diastolic, forces one to mention Addison's disease, but there is nothing else to go with it and I think this electrolyte depletion was merely a part of the acute liver failure.

I would like to see the x-ray films particularly to discover whether the line of the right leaf of the diaphragm is smooth and how much evidence there is for esophageal varices.

Dr. Joseph Hanelin: I think the chest is essentially normal. The right side of the diaphragm is not unusual in appearance. The lungs appear clear. The heart is not enlarged. We have a single spot film of the barium-filled esophagus, and there are definitely wide folds, with undulating contours that strongly suggest varices. I do not know whether there are other films that are more suggestive, but this is almost diagnostic of varices.

Dr. Fairlie: That is strong support for the assumption that she had long-standing liver disease rather than only an acute process — an assumption that is strengthened by the initiation of the final episode with jaundice and ascites but without other symptoms; she was not apparently acutely ill in

other respects. That would be unusual for acute yellow atrophy. The liver was large and very firm, which would likewise be unusual. Further support for the presence of long-standing liver disease is found in the fifteen months' history of nonspecific symptoms and the history of poor nutrition, probable alcoholism and probable esophageal varices.

We thus come to the conclusion that she had portal cirrhosis. What, then, caused her sudden decline? One of the common phenomena that cause cirrhotic patients to become decompensated is infection. This can be an infection of any kind. Even a brief episode of gastroenteritis can be responsible. The white-cell count suggests infection in this patient, but there were no localizing signs. I suppose it could have been a hidden infection, such as mediastinitis, or a deep phlebitis. But there is no reason to think of such entities except that we are searching for infection. Under the heading of infection should be mentioned viral hepatitis. It is uncertain how large a part viral infection of the liver plays in the course of chronic liver disease due to other conditions.

Another common incident precipitating hepatic failure in cirrhotic patients is hemorrhage. It is familiar to see such a patient with acute blood loss shortly thereafter become jaundiced and develop ascites. However, in this patient the stools were guaiac negative; the ascitic fluid was not bloody, and the hemoglobin was 11 gm. per 100 cc. Hence I will dismiss this possibility.

A final consideration, and the one that I think is most likely, is thrombosis of the portal or hepatic veins or possibly of the vena cava. This could account for the sudden development of ascites and jaundice and for the high white-cell count and likewise for the rapid death. Such a thrombosis is sometimes caused by a hepatoma encroaching on the lumen of the vessels. There is little on which to base such a supposition in this case.

I will conclude that the patient had portal cirrhosis. I do not believe the episode leading to her death in hepatic failure was an acute yellow atrophy. The precipitating incident may have been thrombosis of the hepatic portal vein.

Dr. Donald S. King: I saw this patient in the wards for several days before she died. My opinion was that autopsy would show some areas of acute necrosis in the liver in spite of the fact that it was enlarged and apparently hard. I notice that the house officer also suggested that thrombosis would be found at autopsy. We had not thought much about that on the ward. We tried to explain the fever and high white-cell count and diarrhea. We were surprised at the gross autopsy findings, although I do not know what the microscopical findings were.

Dr. John Hogan: Have you seen this electrolyte disturbance in cases of liver disease frequently? The patient was not on salt restriction.

Dr. Fairlie: The numerous cases that came to mind have been the result of therapy, but in a patient with an inadequate diet I believe it could occur even without strict limitation of sodium intake.

Clinical Diagnoses

Laennec's cirrhosis, ? hepatoma of liver.
Cholemia.
Thrombosis of portal or hepatic vein?

Dr. Fairlie's Diagnoses

Portal cirrhosis.
Thrombosis of portal or hepatic vein.

Anatomical Diagnoses

Cirrhosis of liver, alcoholic type, acutely progressive.
Hyperplasia of bone marrow, marked.
Extramedullary hematopoiesis, spleen.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy showed a large, firm, pale and fatty liver, which at first glance seemed smooth but which, when viewed with oblique lighting, could be seen to be finely granular. It cut with resistance, however, and was obviously much tougher than normal. The spleen was only slightly enlarged, weighing 200 gm., and esophageal varices were questionable in our opinion, although I think the x-ray verdict is probably more accurate than ours, since we only see the specimens in the collapsed state. There was nothing else in the gross examination that was particularly remarkable, except the adrenal glands, which were quite swollen, and the bronchi, which contained some purulent exudate.

Microscopical examination of the liver showed a very acutely progressive cirrhosis of the type that we commonly see in alcoholic patients, with moderate amounts of fat and slight diffuse fibrosis, but with a great many cells showing hyaline degeneration and a very unusual degree of infiltration of the liver with polymorphonuclear leukocytes, particularly in the portal areas and about the degenerating liver cells. I would describe it as an alcoholic cirrhosis progressing almost at a fulminating rate — as marked as I have ever seen.

One other surprise was provided by microscopical examination of the bone marrow and spleen. The bone marrow was intensely hyperplastic, with hyperplasia of the red-cell series and quite a considerable proportion of rather primitive cells. It was slightly suggestive of what one sees in pernicious anemia. The spleen also was full of foci of hematopoiesis. I do not know of any certain way of connecting the liver disease and the bone-marrow findings and am inclined to think that the bone marrow was another evidence of dietary deficiency in this patient, rather than being due to the liver condition.

DR. BENJAMIN CASTLEMAN: We have had several patients with so-called acute alcoholic cirrhosis with white-cell counts of 40,000.

DR. MALLORY: Yes; the count can run very high. I do not think we have seen a bone marrow as active as this, and never extramedullary hematopoiesis.

DR. MADELAINE BROWN: I do not suppose you removed a peripheral nerve, did you?

DR. MALLORY: Yes, we did, but the neuropathologist has not yet reported upon it.

DR. HOGAN: The adrenal glands were normal microscopically?

DR. MALLORY: There was lipoid depletion and swelling of the pseudotubular type. It is a nonspecific type of response that one sees in most infectious diseases, as well as in a great variety of noninfective diseases.

CASE 35282

PRESENTATION OF CASE

A forty-eight-year-old man entered the hospital complaining of headache and intermittent vomiting for two weeks. (The history was obtained from the patient's wife because he was drowsy.)

Three and a half weeks before admission he sprayed his apple orchard with a mixture of lead arsenate and DDT; about 35 gallons were used. Three weeks before admission he had an occipital headache, which lasted two days and was relieved by aspirin. A few days later he again sprayed the trees with the same mixture. The spray nozzle broke, and the patient was drenched with the solution. He changed his clothes and finished his work. Two weeks before admission the occipital headache recurred and was more severe. On the following day he started vomiting in a projectile fashion. His doctor found him afebrile, with a strong, slow pulse. Urinalysis showed a few red blood cells. The occipital headache continued, and the patient became lethargic, sleeping most of the time. Ten days before admission he complained of dizziness and weakness on trying to get out of bed and inability to see well without his glasses. Three days later he was admitted to another hospital, where the general physical examination demonstrated no abnormalities. Positive neurologic findings included moderate weakness in the grip of the right hand and weakness of the right leg, but there was no wrist or foot drop. The right knee jerk was greater than the left. The blood pressure was 128 systolic, 80 diastolic, and the pulse 68. The red-cell count was 5,000,000 on two examinations. Two of three blood smears examined reported stippling in 1-400 and 1-500 cells. Five days before admission he seemed irrational and could not answer questions or carry on conversation. On the third and second days before admission he received BAL, and his symptoms cleared up slightly. He was transferred to the Massachusetts General Hospital for further study.

The patient had always been in excellent health until the onset of the present illness except for moderate deafness, present from the age of nineteen. This had been treated recently with pyribenzamine, with some symptomatic relief.

On admission the patient was drowsy and apathetic. The general physical examination was negative except for a pilonidal sinus. The initial neurologic examination demonstrated extreme nuchal rigidity, a negative Kernig sign, bilateral papilledema of two diopters and flaccid paralysis of the right arm and leg, with hypoactive right deep tendon reflexes and normal sensation.

The temperature was 99°F., the pulse 90, and the respirations 18. The blood pressure was 122 systolic, 82 diastolic.

Examination of the urine was negative; a test for arsenic was also negative. Examination of the blood showed a white-cell count of 17,000, with 90 per cent neutrophils, 3 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophils. Occasional stippling of the red cells was noted. The hemoglobin was 14.5 gm. Chemical examination of the blood demonstrated a nonprotein nitrogen of 37 mg., a total protein of 6.6 gm., a calcium of 10.6 mg., a phosphorus of 4.5 mg. and an alkaline phosphatase of 5 mg. per 100 cc. The chloride was 100 milliequiv. per liter. On lumbar puncture the initial spinal-fluid pressure was equivalent to 285 mm. of water, and after 10 cc. of clear, colorless fluid was removed it was equivalent to 95 mm. of water. The total white-cell count was 21 per cubic millimeter, with 7 lymphocytes and 14 polymorphonuclear leukocytes. Globulin reaction was positive, and the sugar was 110 mg. per 100 cc., the chloride 124 milliequiv. per liter, and the total protein 84 mg. per 100 cc. The fluid was sterile.

The patient was placed on BAL therapy, 250 mg. 6 times a day intramuscularly, a high-calcium diet, calcium levalinate (1 amp. intravenously three times a day for two days), syrup of sodium citrate (2 gm. orally four times a day) and 1000 cc. of 5 per cent dextrose and water. For the first three hospital days the patient became more stuporous, drowsy and disoriented. The speech became slurred; he responded to commands slowly and often inaccurately. On the third day neurologic examination showed severe nuchal rigidity and left external rectus weakness, the left eye remaining almost in midposition when the right eye was markedly abducted. The right hemiparesis was severe, involving the proximal as well as the distal muscles, with marked loss of tone and diminished reflexes. No definite facial weakness or anesthesia and no gross sensory loss were detected.

X-ray films of the skull, right hand and arm and a posteroanterior film of the chest were normal. An electroencephalogram showed a diffusely abnormal record, with moderately slow activity, a little more marked on the left than on the right side of the head, especially in the central and, to some extent, the parietal region. The temperature, pulse and respirations went up to 102°F., 130 and 28, respectively. A lumbar puncture on the same day showed an initial spinal-fluid pressure equivalent to 340 mm. of water, with 12 polymorphonuclear leukocytes and 3 lymphocytes per cubic millimeter. The patient was started on penicillin, 100,000 units every three hours intramuscularly, and given 10,000 units of penicillin intrathecally at the time of the lumbar puncture. A ventriculogram on the fourth day showed slightly dilated lateral ventricles, a little more marked on the right. The third ventricle was slightly dilated. The aqueduct and fourth ventricle showed a slight shift to the left, and the aqueduct was also displaced slightly forward. During the day his condition became worse, with a return of rapid pulse to 140, a gradual rise in temperature to 103.6°F. and a continued comatose condition.

At 5:30 p.m. that day he suddenly became cyanotic, with shallow breathing. Oxygen and artificial respiration were started. A ventricular tap showed clear spinal fluid under increased pressure. He died at 5:40 p.m.

Differential Diagnosis

Dr. Robert S. Schwab: Did this man develop the occipital headache before or after the spraying episode, when the nozzle of the hose broke? I think that is an important question.

Dr. William H. Sweet: It occurred after the nozzle broke.

Dr. Schwab: I should like to look at the x-ray films. Where is the pineal body?

Dr. Stanley M. Wyman: I cannot demonstrate it on the anteroposterior or posteroanterior films. In the lateral film it appears to be approximately in the normal position.

Dr. Schwab: I am interested in the statement that the aqueduct was displaced forward and to the left.

Dr. Wyman: The displacement of the aqueduct is best seen in this posteroanterior view. The third ventricle is dilated, lying close to the midline, the aqueduct extending a little toward the left. We filled part of the left ventricle; the right does not seem to fill. The displacement anteriorly is best seen in the occipital position, and the aqueduct can be seen starting horizontally and taking a sharp bend caudally, with a 90° angle at this point. The fourth ventricle is definitely filled. The distal portion of the aqueduct is displaced anteriorly and to the left.

Dr. Schwab: Is the pineal body in normal position in spite of the displacement of the aqueduct?

Dr. Wyman: I cannot see any shift of the pineal body in the anteroposterior view.

Dr. Schwab: The essential clinical findings in a man forty-eight years old with headache, projectile vomiting, stupor and hemiparesis at once suggest intracranial tumor. On the other hand the history given by his wife makes me think of poisoning from heavy metals or DDT. The differential diagnosis is therefore between poisoning from lead, arsenic or DDT, so-called toxic encephalopathy, and tumor. In favor of the diagnosis of poisoning is the temporal relation of this unusual simultaneous exposure to arsenic, lead and DDT (in a 35-gallon amount) some three weeks before admission to the hospital. On the other hand, there is a clue in the statement that the headache in the occipital region came on before he was covered with liquid when the spray nozzle broke. It may be a false clue however. There are several points against poisoning. He was covered with liquid, but he took off his clothes and presumably washed himself so that there was no chronic exposure. He might not have swallowed any of the mixture. For the diagnosis is the report of a small amount of stippling, 1-500 only, on two smears. Outside these two items the picture is not characteristic of heavy-metal poisoning. Against poisoning with metals is the fact that there were no urinary symptoms such as hematuria or albuminuria, which almost always occur in heavy-metal poisoning of the acute type. Also, there was no anemia and no gastrointestinal symptoms such as diarrhea, cramps, colic, nausea and anorexia. There were no skin findings and no lead line on the gums. Patients with arsenical poisoning have dark skin on the hands but no peripheral signs such as sensory loss and wrist drop, which are found with DDT poisoning. However, I have never seen such a case. The administration of BAL evidently failed to do anything because this man continued downhill rapidly and died in spite of medication for heavy-metal poisoning, which he got in large amounts, and in spite of alkalies in tremendous doses. The spinal fluid does not show evidence of meningitis, such as is associated with arsenical poisoning, in which the cells are usually over 100 per cubic millimeter. The stiff neck and the definite rigidity without a Kernig sign or cells in the spinal fluid make me think of a posterior-fossa lesion rather than a meningitis. Another important finding is that this patient was progressively drowsy with aphasia in the end from pressure but was not delirious and did not have convulsions, which are almost always seen in fatal cases of lead encephalopathy before the terminal stage is reached. We have a whole group of points against the diagnosis of heavy-metal or DDT poisoning.

In favor of a tumor of the brain he had had a repeated history of several weeks of progressive drowsiness, headache, choked disks and signs of increased intracranial pressure. There is one point about dealing with the spinal-fluid pressures, the Ayala index — I do not use this index very often, but it may help here. The quantity of fluid removed is multiplied by the final pressure, and the product is divided by the initial pressure. If the ratio is over 5, it is supposed to indicate a diffuse cerebral lesion, with increased spinal-fluid volume. When it is under 5 it is supposed to indicate a space-occupying lesion. With these spinal fluid findings — $\frac{10 \times 95}{285}$ — we have a low index, 3.3, which goes with tumor, probably in the posterior fossa. The spinal-fluid protein of 84 gm. per 100 cc. and the positive globulin are consistent with tumor. The neurologic signs are interesting in that on the third day there was weakness of the left external rectus muscle and right hemiparesis, which suggest that the lesion was near the midbrain but outside it. The air studies suggest something displacing the aqueduct to the left and forward. I think that would be unusual in any poisoning. It suggests tumor in the posterior fossa with pressure in that region. The stiffness of the neck is also consistent with posterior-fossa tumor. Just before death the reduction in reflexes and the hyperthermia would also be associated with a posterior-fossa lesion. A tumor or an aneurysmal sac would be the two things that one would think of. It seems to me, therefore, that the weight of evidence is against poisoning, although I cannot explain the stippling. I should say that he had a lesion of the left posterior fossa near the midline. The x-ray evidence puts it on the other side, which would involve the pyramidal tract from the right hemisphere. Another point worth mentioning is that the seventh-nerve pyramidal fibers cross at the level of the third-nerve nucleus, which would be above the area involved by this lesion. Hemiplegia involving the arm and leg without involving the face is consistent with a posterior-fossa lesion of the left side.

A Physician: Would you consider a secondary metastasis to the brain?

Dr. Schwab: Yes. The data indicated no primary source for the tumor, and the lungs were normal. When I said "tumor" I did not say what kind. It may have been a metastatic tumor. This was a fairly rapidly growing one; it could have been either.

Dr. William H. Sweet: On the ward a nice and lively discussion ensued in this case. From the ventriculograms I said that there was evidence of a space-taking lesion, on the right side of the posterior fossa. Our neurologic colleagues thought that the clinical picture was not sufficiently suggestive of that and took the patient back on their service. I think this case is important to point out again that if one does a ventriculogram, and demonstrates by that procedure a probable neoplasm, there is often very little time remaining for a discussion. The patient must be taken promptly to the operating room, and the neoplasm, if present, treated immediately. In this case we consider that even if there had been a lead encephalopathy, proper treatment was a suboccipital craniectomy for decompression. In the lone case in my personal experience in which lead encephalopathy was so handled the outcome was satisfactory.

Clinical Diagnosis

Tumor or abscess of brain.

Dr. Schwab's Diagnosis

Tumor, left posterior fossa.

Anatomical Diagnoses

Carcinoma of ascending colon, with metastases to brain, liver, lung and lymph nodes.

Arteriosclerosis, generalized, slight.

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy in this case showed something that would not be remotely suggested by the record. The patient had a primary cancer of the ascending colon, with widespread metastases throughout the body.

Dr. Schwab: Was there nothing in the lungs?

Dr. Mallory: Multiple metastases were present in the lungs, which I think should have been demonstrated by x-ray examination. The liver was full of them. As far as the central nervous system is concerned, we found two tumors in the cerebellum — one in the right and one in the left hemisphere. There were two other intracerebral tumors, one in the left parietal and one in the right temporal lobe.

Dr. Schwab: The right temporal and left parietal metastases were apparently silent. Can you see anything in the chest, Dr. Wyman?

Dr. Wyman: I do not see any pulmonary metastases. It is interesting to point out that it is not uncommon to have extensive lesions that cannot be demonstrated on the films. Tuberculosis is certainly a common offender. Could the tumors have caused displacement of the lateral ventricles toward the right in the anteroposterior films?

Dr. Mallory: I think they could have.

Dr. Schwab: Was that a large lesion in the parietal lobe?

Dr. Mallory: No — slightly under 1 cm. in diameter.

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KILLERS IN WHITE

THE collapse of Nazi Germany exposed a series of crimes from which the civilized mind turns in horror. The record of the enormities at Buchenwald, Belsen and Dachau is now complete, but the disclosure has not fulfilled its office if it inspires only disgust and hatred: civilized man must profit from the dreadful lesson both by rejecting the philosophy of the mad dog and by searching for its germ in his own heart.

Elsewhere in this issue of the *Journal*, Alexander describes a most unedifying aspect of a sick society – the genesis of the physician killer. The account of the transformation of men of science into the instruments of a murderous dictatorship is no more shocking than the disclosures of the criminal activities of other professions in the third Reich; indeed, the imagination, sickened by the early and subsequent record of tortures, crematoriums and mass murders, has become so blunted that the full horror is lost upon it. But Alexander, in his description, traces the unholy progress of German medicine in terms that leave no room for indifference: if men dedicated to the most merciful of callings, with a record of splendid achievement, could in a few years become the tools of those who lived by calculated tortures and killings, what wonder that the rest of the nation came to accept murder as an instrument of state policy?

They are all pictured: the scientist who developed the most efficient method of extermination by gas; the physician who grew enthusiastic over the "wonderful material among those brains, beautiful mental defectives, malformations and early infantile disease"; the psychiatric expert who chose the victims for the killing centers; the investigator who performed experiments whose success depended on the death of the test subject; the specialist in poison and death by intravenous injection; and the man who used human subjects "for tests that were totally unnecessary, or whose results could have been predicted by simple chemical experiments." The only one missing is the physician who may in conscience have deplored the excesses of the Nazi regime, especially in their application to medicine, but who refrained from opposition or public disapproval – it will perhaps never be known how many physicians, like their fellows among the lay public, belonged in this category. One of the most tragic conclusions is expressed in the words, "Whatever methods he used, the physician gradually became the official executioner, for the sake of convenience, informality and relative secrecy."

But the main value of this study is its implication that the descent of the doctor to the level of the gangster can happen in any country. The embracement of the utilitarian philosophy of Hegel, with its corollary of euthanasia, has its counterpart in American society — Dr. Alexander cites chapter and verse in the form of the attitude of a physician and a hospital toward patients with chronic degenerative disease; he emphasizes the discussion of sterility and euthanasia at a meeting

of Bavarian psychiatrists before the rise to power of the Nazis.

The moral is unmistakable, but hope and confidence can also be drawn from this depressing account. To show that the Hegelian attitude is not making headway unopposed, the author points out the developments that counteract such a trend: the societies of patients with chronic disease who dedicate their lives to the guidance and information of fellow sufferers, with the inspiration and direction of the medical profession. This fact, Dr. Alexander states, is having "an extremely wholesome effect in introducing fresh motivating power into the ivory towers of academic medicine."

The history of the complete brutalization of an eminent profession contains information that is instructive and sobering. The advancement of science must proceed, but not at the cost of the humane considerations that are the epitome of medical practice. It is to be hoped that American medicine will proceed to still greater heights of achievement, avoiding alike the "newly acquired delusions of omnipotence" described by Dr. Alexander and the Judas cry of the guiltiest of men, "Is it I, Lord?"

ESSENTIALLY USELESS

THE use of the right word at the right time is an accomplishment to which most medical writers and speakers aspire. Oddly enough, familiar words seem to be more frequently misused than unfamiliar ones. The speaker or writer is more inclined to resort to the dictionary for the meaning of the latter but often feels falsely confident with regard to the former.

Certain words and phrases are vastly overworked by medical users and so indiscriminately are they employed that any special meaning they may originally have possessed has by now been lost. One such word is the modifier *essentially*, which has come to be considered indispensable in case presentation whether written or spoken. At some time in the past, the word probably was used for a specific purpose, but at present it seems to be anything but indispensable. One hears that a physical examination or a chest plate, or an abdominal exploration, or a battery of laboratory studies is *essentially* negative. It is inserted because it is considered to protect the user from criticism. In a case of coronary vascular sclerosis, for example, there may be no cardiac enlargement, murmurs, or irregularities of rhythm; the liver is not enlarged and there is no peripheral edema. For these reasons, one may consider that there are no significantly abnormal physical findings, but is afraid to say so. If he does, a listener may leap to his feet and scold him for not noting that there is a *musca volitans* in the right eye and that quite obvious signs of epidermophytosis would have been found had he bothered to look between the toes. The prepared defense against such onslaughts is to say that the physical examination was *essentially* negative or noncontributory. A moment's reflection should convince one that the insertion of the magic word protects him from nothing. If irrelevant details are omitted in a case presentation thoroughly sensible precedent is merely being followed. If truly significant details are omitted neither the word *essentially* nor any amount of linguistic adroitness can protect the speaker from criticism.

Uncritical use of the language is not necessarily a sign of uncritical scientific thinking, but such use is not infrequently its bedfellow. Insistence on precision, tiresome though it may seem, will eliminate a surprising amount of useless and taxing verbiage. The word *essentially* is merely one example among many.

TOP-HEAVY PAYROLL

AT January's end, according to the *New York Times*, the Civil Service Commission reckoned the employees of the executive department of the federal Government at 2,094,777. The figure represents a gain during the year of 90,803 — a gain that may be counted largely as a loss to the taxpayer.

Government's busy civilian workers are distributed somewhat as follows; 75,000 in the three military departments; 500,000 in the post office; 200,000 in the Veterans Administration; 89,000 in the Treasury Department; 70,000 in the Department of Agriculture; 45,000 in the Department of the Interior, down to only 3,400 in the

Department of Labor — a mere handful. Veterans constitute 47 per cent of all federal employees.

There is a certain fascination in the spectacle of a nation strangling itself by paternalism. The process can be stopped only by a mass reaction, and yet if it continues the outcome is inevitable.

Smallpox is again showing itself in different sections of Maine. More persons die of this disease, who are natives of that State, it is asserted, than in all the rest of New England. So much for neglecting vaccination.

Boston M. & S. J., July 11, 1849

NOTES FROM THE MEDICAL EXAMINER

IDENTIFICATION OF BLOODSTAINS—I

There are few types of evidence that occur with greater regularity at the scenes of crimes of violence and bear implications of greater evidential importance than bloodstains. Their recognition and characterization serve to localize the scene of the crime, aid in determining the manner in which it was committed and, if circumstances are favorable, help to identify the perpetrator. It is therefore valuable to review current methods of blood identification and their application to legal medicine.

The most sensitive tests for blood are those which make use of its catalytic activity in enhancing the oxidation of certain phenols and amines by hydrogen peroxide. These reactions, which the benzidine, guaiac and phenolphthalein tests[1-3] exemplify, depend upon the blood peroxidase activity, an enzymatic function of the heme portion of the hemoglobin molecule. The reactions are extremely sensitive. Thin, invisible dried smears, caused by as little as 1 part of blood in 10,000 parts of water, may be detected by the benzidine test,* for example. Even garments that have been laundered several times may yield evidence of previous bloodstains.

Unfortunately, no one of these tests is by itself specific for blood. Vegetable peroxidases, such as those present in horseradish, potato and turnip, cause similar reactions and may be destroyed by boiling, whereas the peroxidase activity of blood is relatively stable. But the virtue of the catalytic blood tests, of which the benzidine test is the most generally practical for medicolegal purposes, rests in their high sensitivity and simplicity. They are best used for screening purposes, not for proof. If the test is negative, blood is absent; if it is positive, blood is suspected. The following case provides an example to illustrate the point.

A 64-year-old retired businessman, his wife and her elderly sister, who lived in a single house in a residential suburb, had not been seen for several days. The apprehension of neighbors having been aroused, the house was entered through a window. The 2 women were found in bed beaten to death, and the man hanging by a rope around the neck in the cellar. The extent of blood splashes at the scene of the death of the women indicated that their assailant had been blood splattered. The man was clean and dressed in a lounging robe and fresh pajamas. Benzidine tests of the hands and body of the man revealed abundant evidence of washed blood. The wash basin in the bathroom also revealed invisible blood stains. The evidence substantiated the fact that the man had committed suicide by hanging after murdering the women.

Bloodstains remain detectable on the hands, arms and body of a living person for several days, in spite of ordinary careful washing. This fact is of considerable importance in the examination of suspects in murder cases, sex offenses and other bloody crimes of violence. The reagent may be applied directly to the skin, or the skin may be swabbed by moistened filter paper, to which the reagent is then applied. In examination of a person for bloodstains, it is important to keep in mind the possibility of local stains (without criminal implication) arising from chapped hands or lips, pimples, minor cuts and abrasions.

For medicolegal purposes it is desirable to establish the presence of blood with greater certainty than can be done by the catalytic tests. Spectroscopic examination and microcrystal tests add confirmatory, and frequently conclusive, evidence. Because the spectroscopic examination requires relatively large amounts of blood, it is not applied so frequently as the microcrystal tests. The Bertrand[4] modification of the hemin crystal test† and the hemochromogen crystal test‡ are applicable to any blood particle or stain that can be seen by the naked eye. Each test may be carried out on a microscope slide, the resulting crystals being examined under the microscope. In favorable cases the characteristic spectral absorption of the hemochromogen crystals may be confirmed by the use of a microspectroscope.

*The benzidine reagent consists of 0.1 gm. of benzidine and 0.2 gm. of sodium perborate dissolved in 10 cc. of 50 per cent acetic acid. It should be prepared immediately before use. An instantaneous blue color indicates blood.

†Reagent: 1 gm. of magnesium chloride, 1 cc. of water, 5 cc. of glycerin and 20 cc. of glacial acetic acid. A drop of reagent is added to the blood particle on a microscope slide and covered with cover slip and heated gently, nearly to boiling. It is cooled, reheated and then cooled and examined under low power. Brown rhombic plates of hemin are observed.

‡Reagent: 6 cc. 10 per cent sodium hydroxide, 6 cc. of pyridine, 6 cc. of saturated solution glucose and 14 cc. of water. The reagent improves with age and then deteriorates. One drop is added to the blood particle on a microscope slide, and a cover slip is applied. The slide may be warmed very gently to induce crystal formation. Characteristic, salmon-pink, nearly rhombic plates occur.

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